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ORGANIC SEMINAR ABSTRACTS

1969-70

Semester I

Department of Chemistry and Chemical Engineering

University of Illinois

Urbana, Illinois



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SEMINAR TOPICS

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THE ADDITION OF CARBON-CARBON MULTIPLE BONDS TO THE "BENT"  
BOND OF BICYCLO[2.1.0]PENTANE

Reported by Edward G. Saurborn

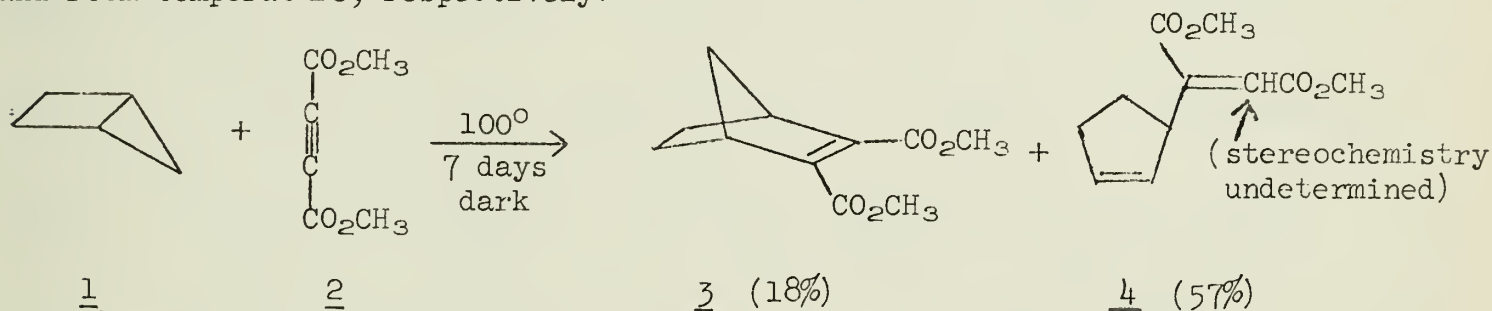
September 18, 1969

INTRODUCTION

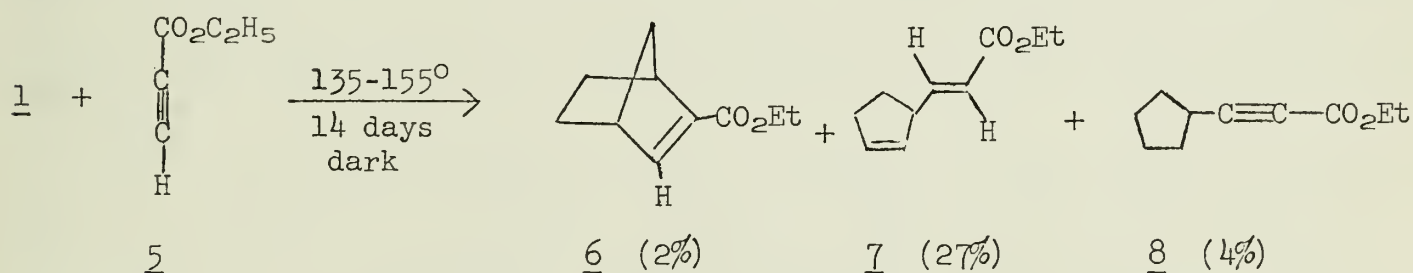
The first synthetic preparation of bicyclo[2.1.0]pentane was reported<sup>1</sup> in 1957. Since then, this compound has received considerable attention due to the high reactivity of the 1,4-σ bond. The strain energy of this bridge bond is even greater than that of the 1,3-σ bond of bicyclobutane, as evidenced by the respective heats of hydrogenation<sup>2,3</sup> (47.4 kcal/mole vs. 41.3 kcal/mole) for the two bridge bonds. The reactions of bicyclopentane reflect those of a cyclopropane, but the prevailing influence is that of the strain relief offered by the cleavage of the "bent" bridge bond. In the literature, the following types of reactions have been noted:<sup>4</sup> thermolysis, which involves opening of the 1,4-σ bond; hydrogenation, addition of electrophiles such as strong acids and metal salts, and halogenation, each of which results in addition across the bridge bond; treatment with base, which generates a mixture of bicyclo[2.1.0]pentyl-1- and bicyclo[2.1.0]pentyl-5-carbanions; and the addition of acetylenes and olefins. The last type of reaction is the subject of this seminar.

THE REACTIONS OF BICYCLO[2.1.0]PENTANE WITH ACETYLENES AND OLEFINS.

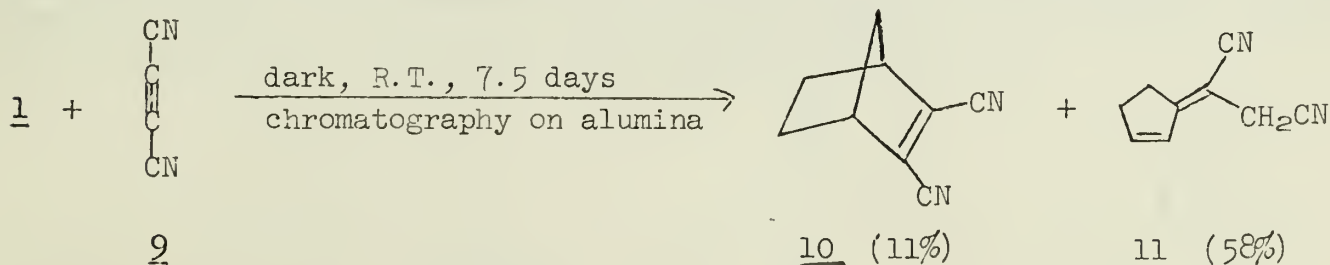
Gassman and co-workers have reported<sup>5,6</sup> that bicyclopentane has been treated with dicarbomethoxyacetylene, ethyl propiolate, and dicyanoacetylene at 100°, 135-155°, and room temperature, respectively.



The reaction of 1 with ethyl propiolate (5) gave two products (6 and 7) with structures analogous to the products of the preceding reaction, and an additional product (8).



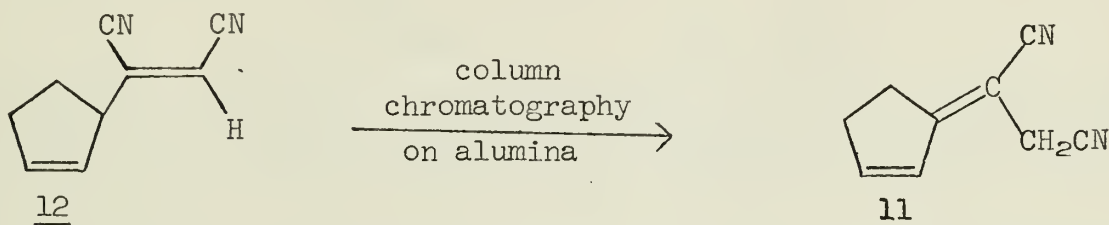
In the reaction of 1 with dicyanoacetylene, it was observed that the double bonds were conjugated in 11, rather than non-conjugated as in 4 and 7. The crude



reaction mixture was then investigated and found to show ultraviolet absorptions at 249 (due to 10) and 229 mμ. The absorption which 11 shows at 265 mμ was completely



absent. This indicated that the initial reaction product might be similar to 4 and 7, and indeed, this was the case, in that the major product was actually 12 (ultra-violet maximum at 229 mμ, ε 14,400). Compound 12 was isolated via liquid-liquid partition chromatography, and subsequently shown to rearrange to 11 when chromatographed on alumina. In these reactions, the structures of 3, 6, and 10 were



proven by independent syntheses and those of 4, 7, 8, 11 and 12 established by degradative and spectroscopic studies.

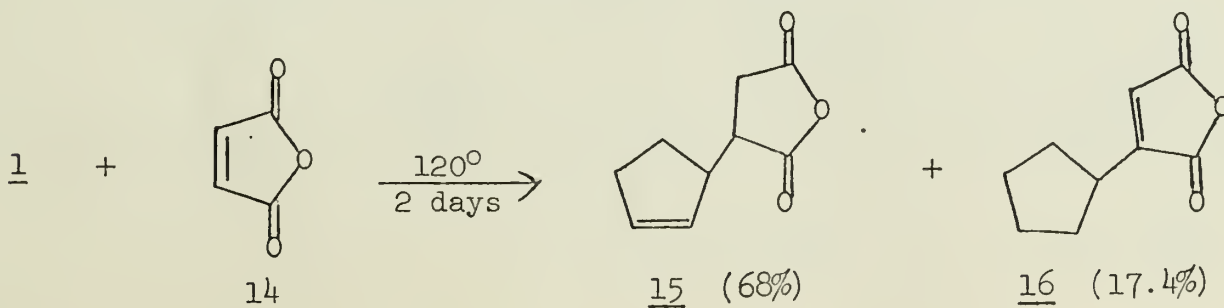
In this series of reactions, it should be noted that: (a) each reaction gave a 3-substituted norbornene as a minor product, which can be visualized as a cycloadduct; (b) each reaction gave a 3-cyclopentenyl-olefin as the major product; (c) of the three major products,<sup>8</sup> two (7 and 12) had stereochemistry resulting from cis-addition, and that of 4 was undetermined; and (d) each acetylene was substituted with a strong electron-withdrawing moiety, capable of conjugative stabilization of a transition state.

To test the dependence of the reaction on the acetylene substituent, the reaction of bicyclopentane and diphenylacetylene was attempted, but did not occur. As a complementary reaction, 1 was exposed to perfluoro-2-butyne, and again, no evidence of reaction could be detected.

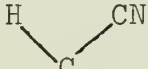
It was therefore concluded that while electron deficiency of the acetylene is a critical requisite, it is not a sufficient cause for reaction to occur; resonance stabilization of the transition state must also be crucial.

To test the dependence of the reaction on ring strain, another reaction of a suitably substituted acetylene and a strained cyclopropane was investigated. In the literature, bicyclo[3.1.0]hexane (13) has been shown to be slightly less reactive than 1 in that reactions of 13 with mercuric acetate,<sup>9</sup> acetic acid,<sup>10</sup> lead tetraacetate<sup>11</sup> and thallium triacetate<sup>11</sup> show more external (i.e., 1,6-bond) cleavage than internal (1,5-bond) cleavage, whereas 1 shows only internal (1,4-bond) cleavage under these conditions. If 13 were to react with 2 in the same manner as the above cleavage reactions, then the reaction of 1 with 2 could be assumed to have no more dependence on ring strain than the reactions of 1 with the various metal acetates. However, exposure of 13 to 2 gave no reaction. It was therefore concluded that the cyclopropane has to possess considerable strain if a facile reaction is to occur under relatively mild conditions.

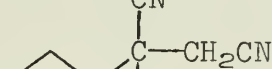

The reaction of bicyclopentane (1) with maleic anhydride (14) was investigated<sup>12,13</sup> as a probe into the stereochemistry of the additions of carbon-carbon multiple bonds to the bridge bond of 1. In order to obtain a clear picture of the mechanism of the additions of both electron-deficient acetylenes and electron-deficient olefins to bicyclopentane, it is necessary to ascertain from which direction (i.e., above or below the "flap") the carbon-carbon multiple bond attacks the bridge bond of 1. When 1 is treated with 14 at 120° for a period of 2 days, 15, 16, 17, and 18 are obtained. The structures of 15, 17 and 18 were verified by comparison with authentic samples, that of 16 was established by degradative and spectroscopic studies.





$\underline{1} +$ 

 $\xrightarrow[85\%]{a}$

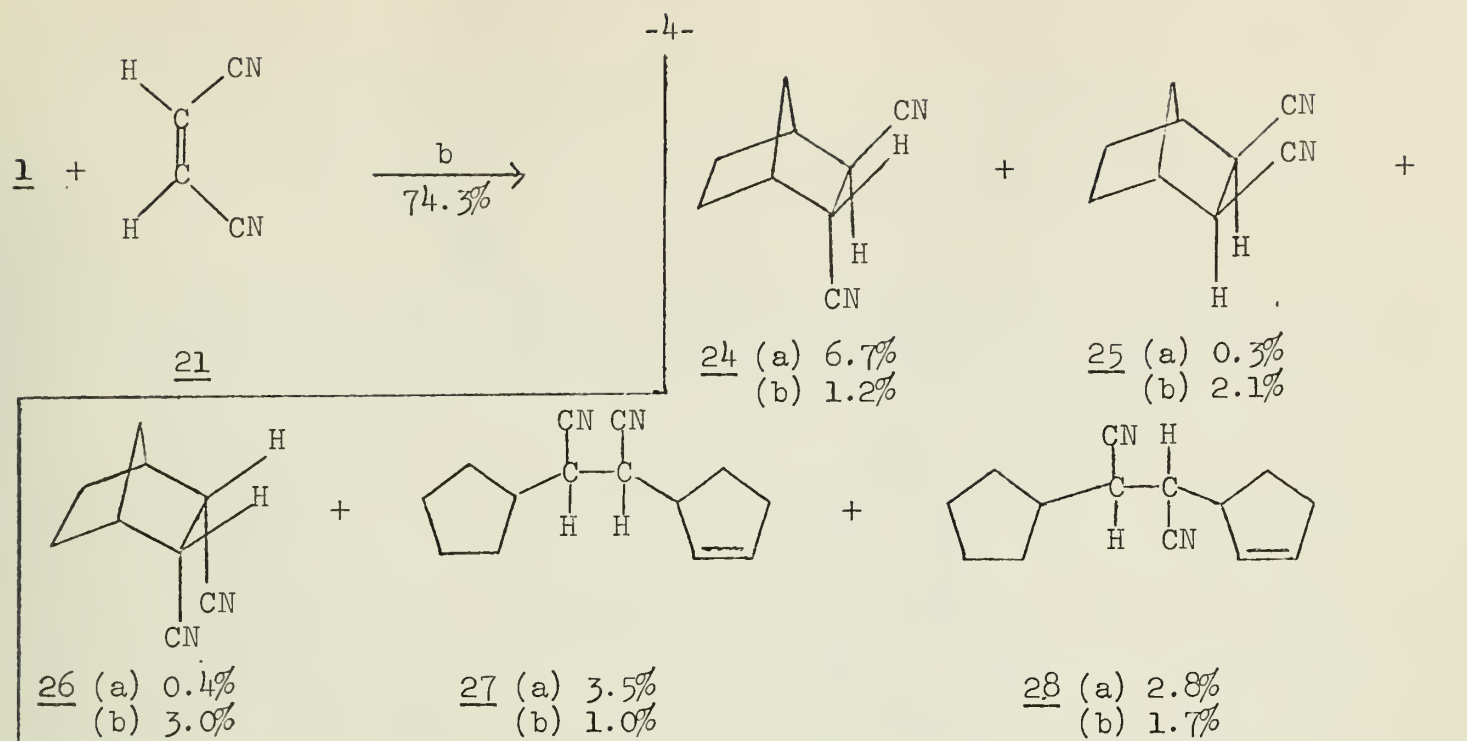
$\underline{20}$


 $+$ 

 $+$

$\underline{22}$  (a) 80.0%  
 (b) 88.7%

$\underline{23}$  (a) 6.2%  
 (b) 2.2%





# THE MECHANISM OF THE ADDITION OF ELECTRON-DEFICIENT ACETYLENES AND OLEFINS TO THE 1,4-BOND OF BICYCLO[2.1.0]PENTANE

Mechanistically, these reactions could occur via either a concerted multicenter reaction or a stepwise process, with the latter involving either zwitterionic or diradical intermediates. (Evidence suggesting diradical intermediates in the reactions of bicyclobutane derivatives and olefins has been observed.<sup>17,18</sup>) With this in mind, a kinetic study of the reaction of bicyclo[2.1.0]pentane (1) and dicarbomethoxyacetylene (2) was undertaken.<sup>7</sup> The reaction was determined to be cleanly first order in 1 and 2 when run in each of three different solvents. The data obtained are given in Table I.

Table I

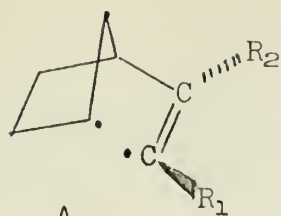
Solvent	Dielectric Constant	$k \times 10^4$ (l m <sup>-1</sup> sec <sup>-1</sup> )	k(rel)
Benzene	2.27	1.08 ± 0.03	1.46
Ethyl acetate	6.03	0.74 ± 0.02	1.00
Acetonitrile	37.5	1.37 ± 0.03	1.85

If a zwitterionic intermediate were involved in this reaction, a change of rate of 10<sup>3</sup> to 10<sup>6</sup> might be expected.<sup>19,20,21</sup> Since the observed factor is less than 2, the possibility of a zwitterionic intermediate is, for all practical purposes, eliminated by this lack of a solvent effect.

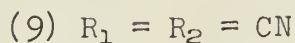
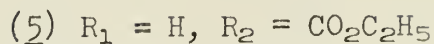
The possibility of a concerted multicenter reaction mechanism is opposed by the following observations: (a) The rates of reaction of 1 with 2 at 35°, 2 at 100° and 5 at 135° were comparable. If only inductive parameters are considered, perfluoro-2-butyne, which is an excellent Diels-Alder dienophile, and is comparable to dicyanoacetylene as an electron-deficient dienophile,<sup>22,23</sup> would be expected to react with 1 below 100°. But when 1 was exposed to perfluoro-2-butyne at 100° for a period of 3 days, no evidence of reaction was observed. This result is most consistent with a mechanism involving formation of a diradical species in which conjugative stabilization of the intermediate radical is of considerable importance. (b) Since mixtures of the three norbornanes (24, 25 and 26) were obtained in both of the reactions of bicyclopentane and fumaronitrile (20) or maleonitrile (21), the reaction must have proceeded via a mechanism which allowed rotation about the central bond of the nitriles. Therefore, an intermediate must have been generated which was able to undergo this rotation. The demonstration of the presence of this intermediate requires a two-step mechanism.

If the reactions do occur via a diradical mechanism, the reaction of 1 and the acetylenes would involve the diradical intermediate A. In subsequent fast steps, the

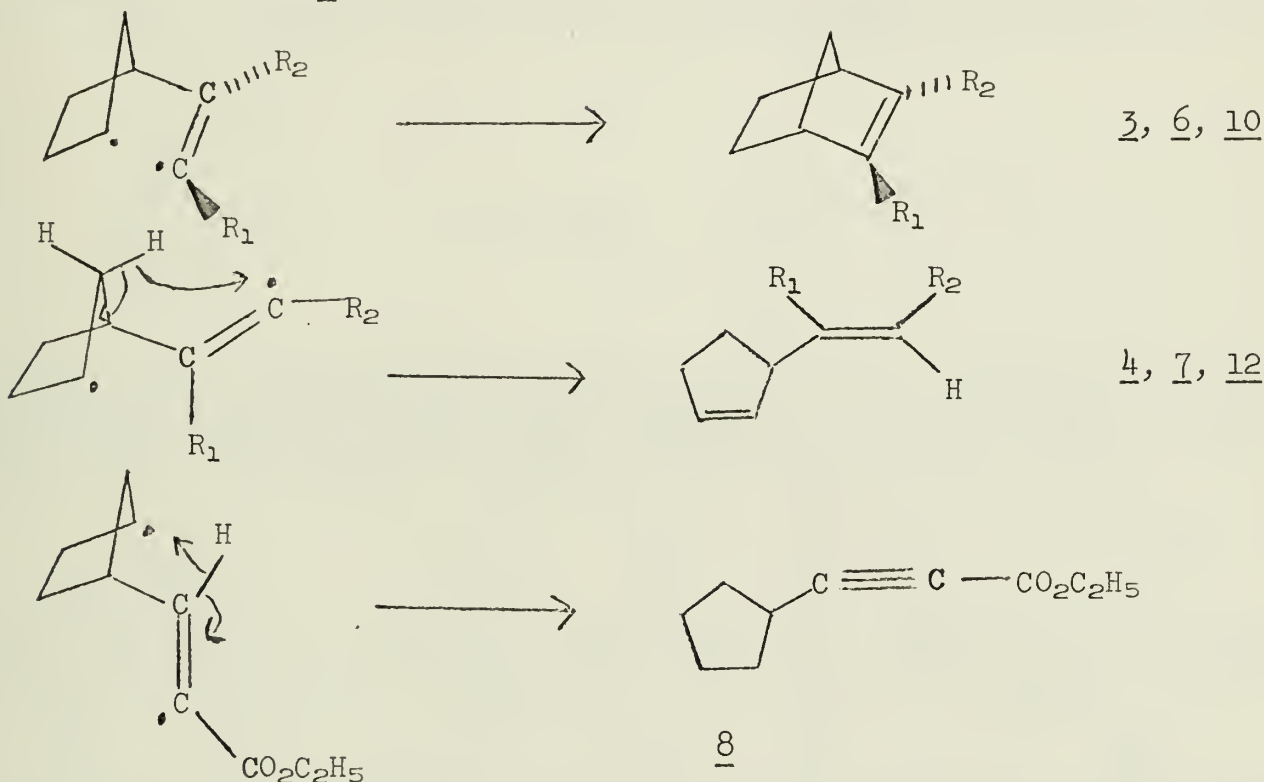




A

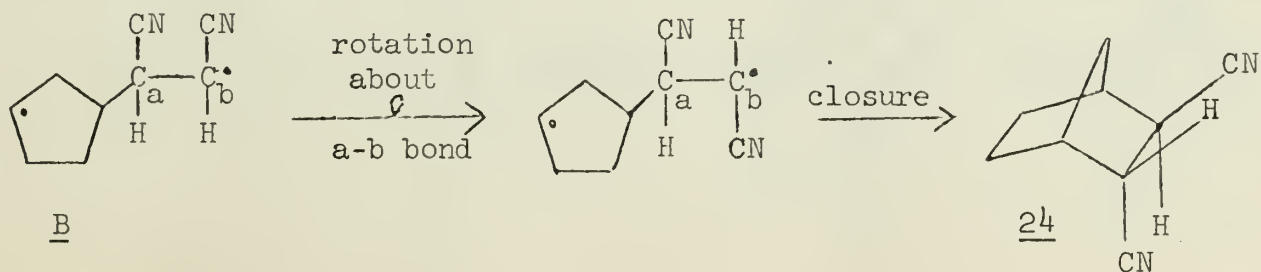


intermediate diradical could partition between the cycloadduct and homoene product. In the reaction of 1 and ethyl propiolate (5), the formation of the third product (8) is readily visualized from A.

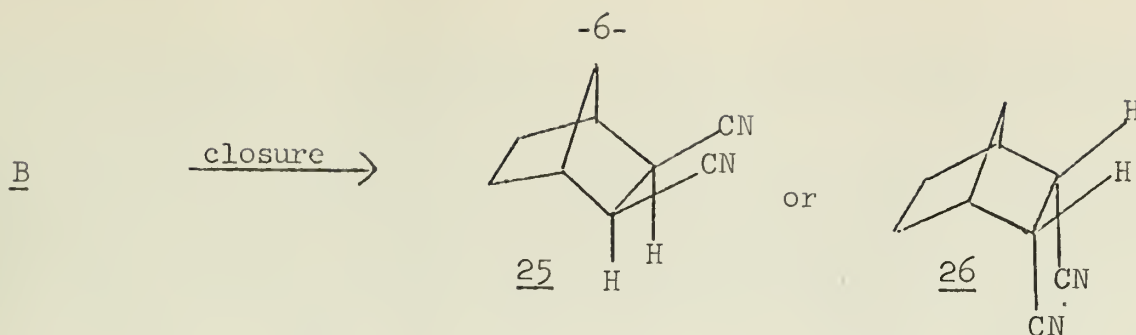


Since the conformation of A, which is determined by rotation about the newly-formed carbon-carbon  $\sigma$  bond, dictates which product (i.e., cycloadduct or homoene) results, this rotation and the radical combination must be competitive reactions, occurring at extremely fast rates. The formation of cycloadduct and homoene products is therefore rationalized by the fact that in simple cases the activation energies for combination and disproportionation of radicals have been found to be nearly equal.<sup>24</sup> Also, Bartlett has shown<sup>25-28</sup> that intramolecular combination of a diradical is competitive with rotation about a carbon-carbon single bond (i.e.,  $k \approx 10^{10} \text{ sec}^{-1}$ ). Competitive reactions occurring at extremely fast rates, such as radical combination and disproportionation should have such low activation energies as to be impervious to the environment. Thus, a solvent effect would not be expected in these intramolecular reactions of diradicals, which is consistent with the results.

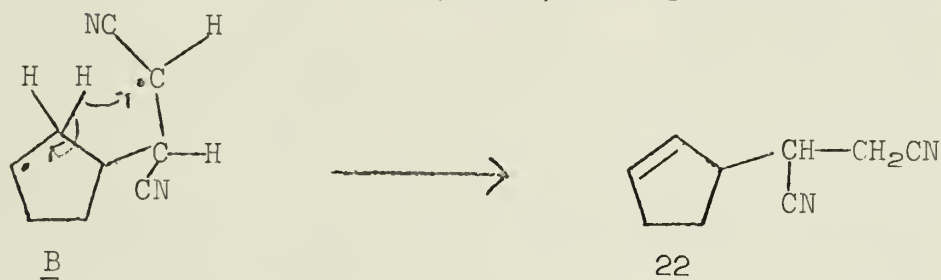
If one will accept the premise that both the acetylene and olefin additions occur via the same mechanism, then the possibility of a zwitterionic intermediate is eliminated by the lack of solvent effect on the reaction of 1 and dicarbomethoxyacetylene. Thus, in the reactions of 1 and the olefins 20 and 21, a diradical intermediate (B) can be visualized which would lead to 24, 25 and 26. Rotation about the  $\text{C}_a\text{-C}_b$  bond would be expected to be competitive with ring closure of the diradical to give norbornane derivatives.<sup>25-28</sup>



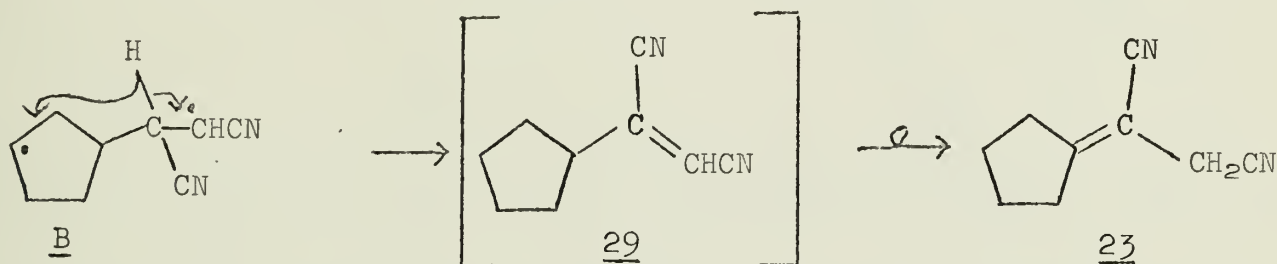




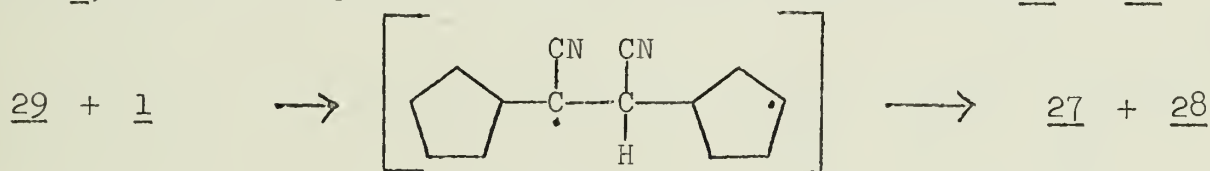
Formation of 22 would then occur in the same manner as the formation of the homoene products in the acetylene reactions, i.e., hydrogen abstraction from the ring of B.



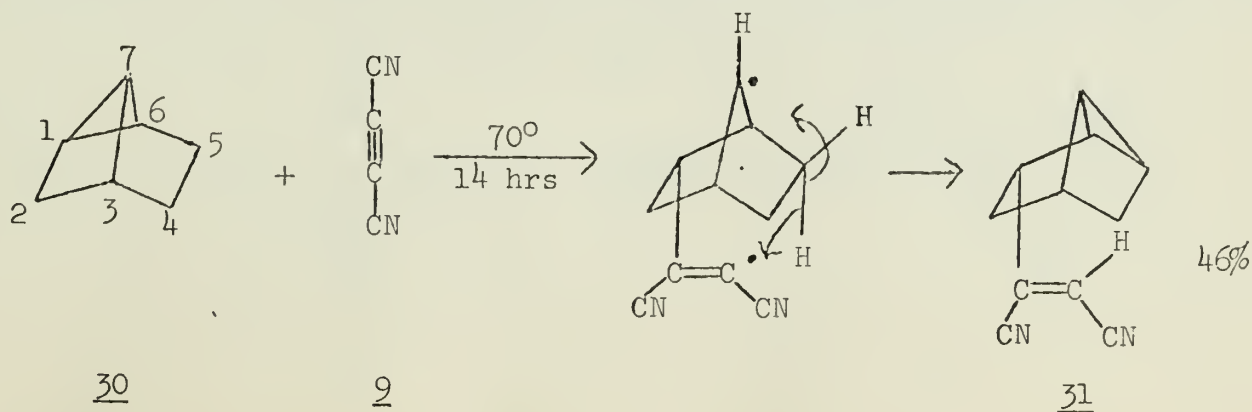
Analogous to the reaction of dicyanoacetylene and 1, which yielded a rearranged product, 11, the postulated intermediate B could transfer a hydrogen to the ring to form 29, which could rearrange to 23. This type of hydrogen transfer (to the ring) was observed in the reaction of 1 and propiolic ester (5) to form 8.



A further indication of the formation of 29 is the presence of 27 and 28, which could arise from the addition of 29 to a second molecule of 1. In this reaction, the relative amounts of 27 and 28 were found to be extremely dependent upon the concentration of 1, which was employed in a 1.8:1 ratio to the nitrile 20 or 21.



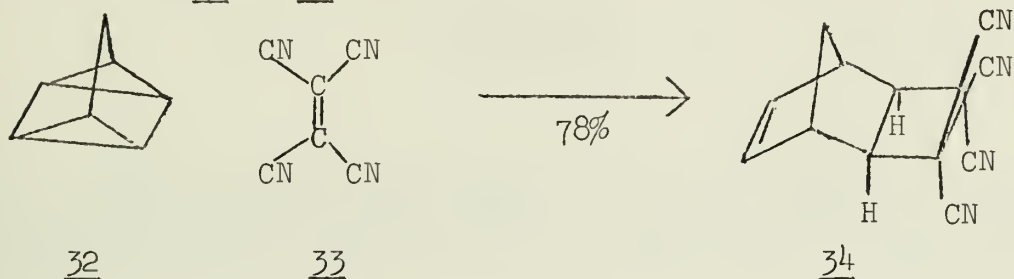
This type of diradical intermediate can be utilized to demonstrate the extent of steric control exhibited by the bicyclopentane towards the attacking carbon-carbon multiple bond. This further indicates the preference for attack under the flap of the bicyclopentane. In fact, this mode of "backside" attack of the bridge bond is a general phenomenon insofar as the same mode of attack is observed<sup>29,30</sup> with derivatives of bicyclo[1.1.0]butane. This example involves the addition of dicyanoacetylene to tricyclo[4.1.0.0<sup>3,7</sup>]heptane<sup>31</sup> (30), in which the product structure was proven via chemical and



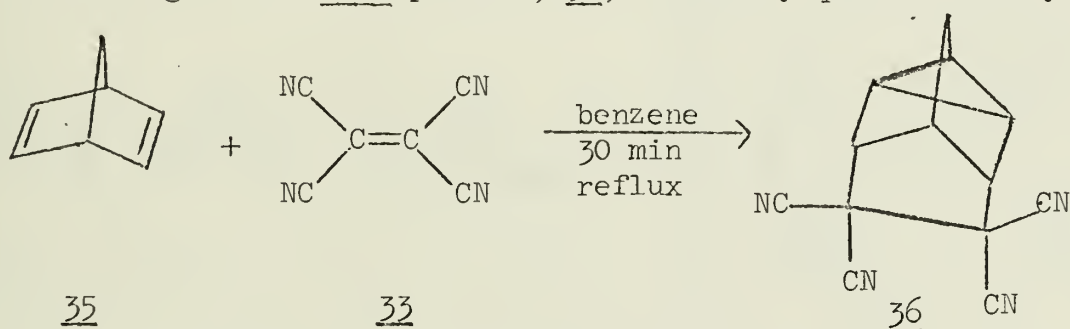


spectroscopic analysis. Not only does this reaction show rear attack on the 1,7-bond, it also demonstrates that while steric hindrance does not overcome this tendency, it does control which end of the  $\sigma$  bond is attacked.

An interesting example<sup>32</sup> of this addition of electron-deficient carbon-carbon multiple bonds to bicyclopentane is found with quadricyclane (tetracyclo-[3.2.0.0<sup>2,7</sup>.0<sup>4,6</sup>]heptane), 32. Since only the exo-product, 34, was obtained, the initial attack of 33 on 32 must have occurred from inside the "flap."

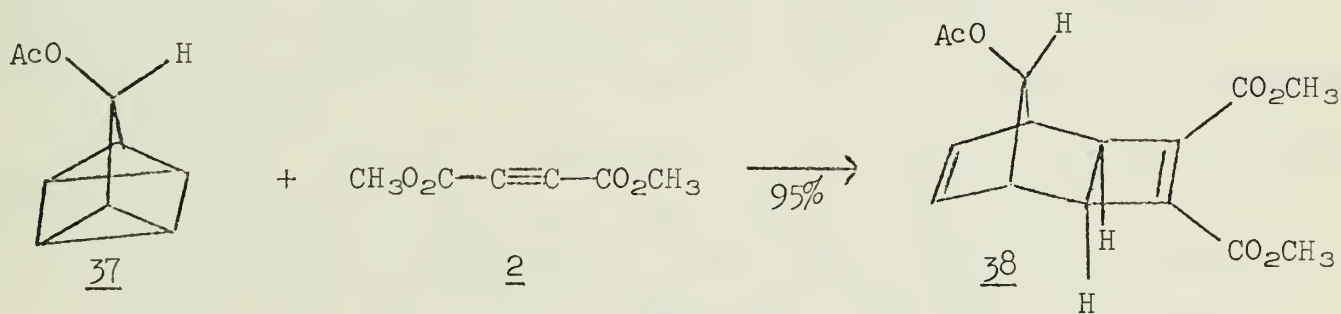


In contrast with this reaction, it should be noted that tetracyanoethylene adds to norbornadiene to give the endo-product, 36, in nearly quantitative yield.<sup>33</sup>



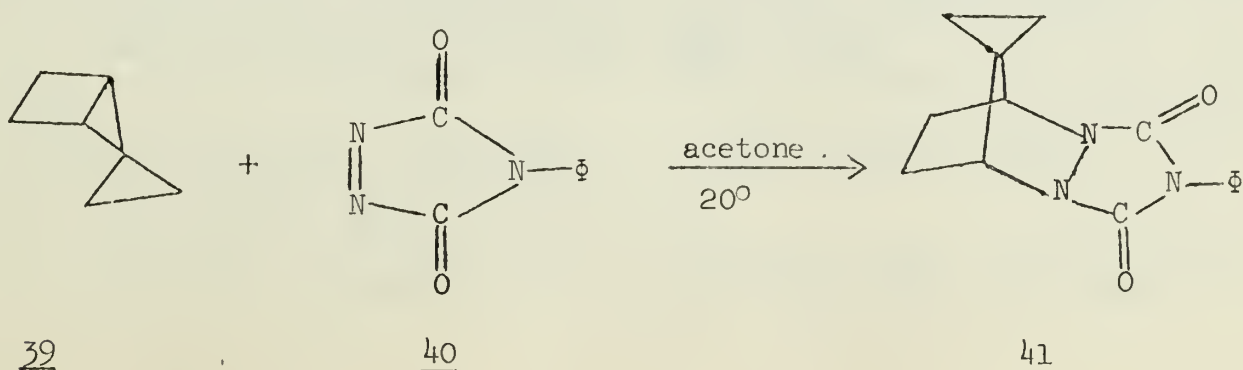
Results<sup>32</sup> analogous to those of the quadricyclane and tetracyanoethylene reaction were obtained when 32 was treated with 2, 9 and methylpropiolate, as again, only exo-products were found.

In the reaction of 30 with 9, it was noted that steric factors can determine which end of the bridge bond is attacked. Similarly, substituents at the 7-position of quadricyclane can direct which side of this molecule is attacked.<sup>32</sup>



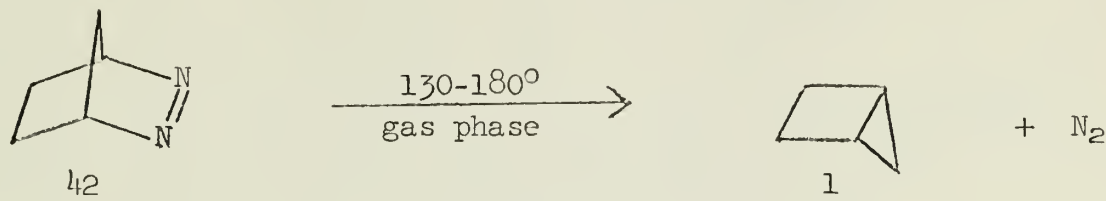
#### THE REVERSE REACTION

In the investigation of the formation of 2,3-diaza-bicyclo[2.2.1]heptane, it has been shown<sup>34</sup> that the reaction of bicyclo[2.1.0]pentan-5-spiro-cyclopropane, 39, and 4-phenyl-1,2,4-triazoline-3,5-dione, 40, is stereospecific (+2%) and proceeds by inversion of configuration at the bridgehead carbons. Since the stereochemistry of this addition

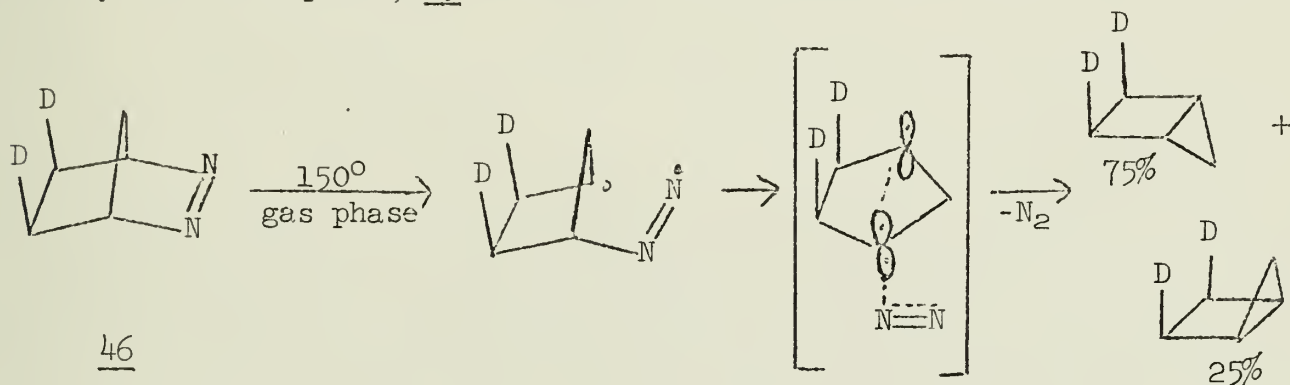




is the same as that of the addition of electron-deficient carbon-carbon multiple bonds to bicyclo[2.1.0]pentane, it is of interest to consider the mechanism of decomposition of 2,3-diaza-bicyclo[2.2.1]-2-heptene, 42, which has been shown<sup>35</sup> to give first order kinetics in a non-catalyzed, homogeneous gas phase reaction. Although an alkyl di-radical was first postulated<sup>1,35</sup> as the intermediate for this reaction, later work has



shown<sup>15,34,36</sup> that the stereochemistry of the decomposition is identical with that of the addition and allows the same transition state. The most likely mechanism has been postulated by Roth and Martin<sup>34</sup> for the decomposition of exo-4,5-dideutero-2,3-diaza-bicyclo[2.2.1]-2-heptene, 43.



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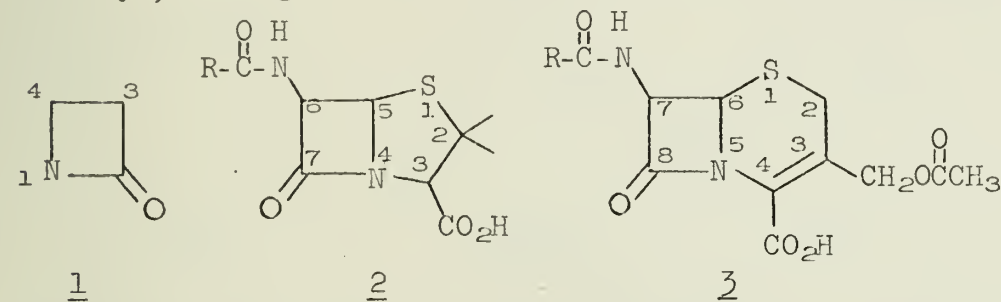


# THE SYNTHESIS OF $\beta$ -LACTAMS

Reported by John A. Secrist III

September 22, 1969

The synthesis of  $\beta$ -lactams, or 2-azetidinones (1), has received considerable attention since the 2nd World War, when it was learned that this ring system was contained in the penicillin (2) structure. Since that time another series of antibiotics, the cephalosporins (3), has also been found to contain the  $\beta$ -lactam ring. Synthesis of these two antibiotics, and related compounds, has provided the major impetus for the continuing emphasis on the  $\beta$ -lactam ring. The conventional schemes for lactam synthesis can not be applied to  $\beta$ -lactams, due to the ring strain and the high reactivity of the carbonyl, making the ring highly susceptible to cleavage.



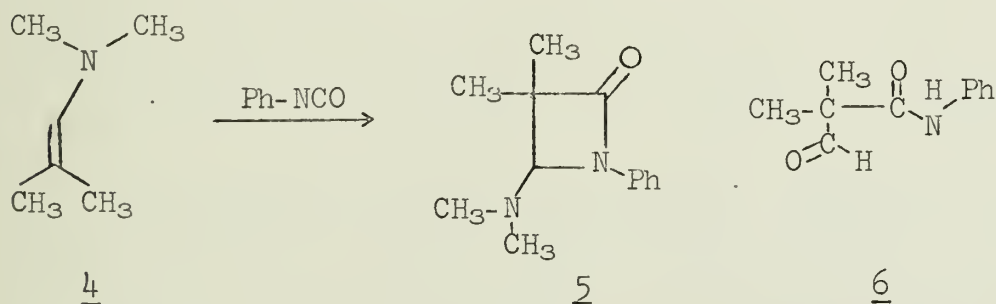
In 1958 Sheehan and Corey reviewed the methods which had been used up until that time for the synthesis of  $\beta$ -lactams.<sup>1</sup> It is the purpose of this seminar to survey the major new methods which have been applied since that time to the synthesis of these compounds,

covering the literature in terms of general classes of reactions.

Identification of all the reported  $\beta$ -lactams was made primarily on the basis of elemental analysis and infrared spectroscopy. The  $\beta$ -lactam carbonyl has a very characteristic band at  $1755\text{ cm}^{-1}$  to  $1810\text{ cm}^{-1}$  which can be used to distinguish it from other types of products. In many cases nmr, mass spectral, ultraviolet, and degradative evidence also were used for further structure confirmation.

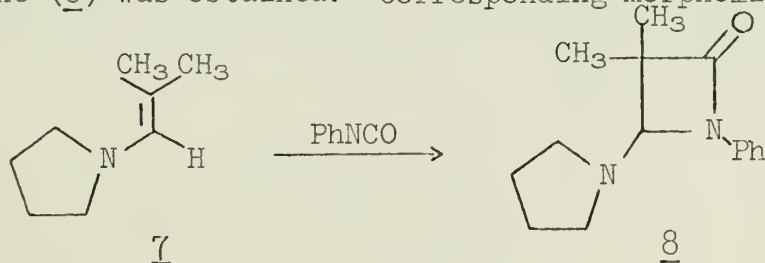
## REACTIONS UTILIZING ISOCYANATES

Perelman and Mizsak found that  $\beta,\beta$ -disubstituted enamines react with isocyanates to give the corresponding  $\beta$ -lactams.<sup>2</sup> This synthesis was the first in which the carbonyl to C<sub>3</sub> and nitrogen to C<sub>4</sub> bonds were formed simultaneously. Equimolar quantities of N,N-dimethylisobutenylamine (4) and phenyl isocyanate react to yield the  $\beta$ -lactam 1-phenyl-3,3-dimethyl-4-dimethylamino-2-azetidinone (5).



Utilization of enamines with a  $\beta$ -hydrogen results in the formation of  $\beta$ -ketocarboxamides related to 6, with no evidence of  $\beta$ -lactam formation during the reaction. At nearly the same time, Opitz and Koch<sup>3</sup> applied this reaction to a different set of enamines. In the case of 1-pyrrolidinoisobutene

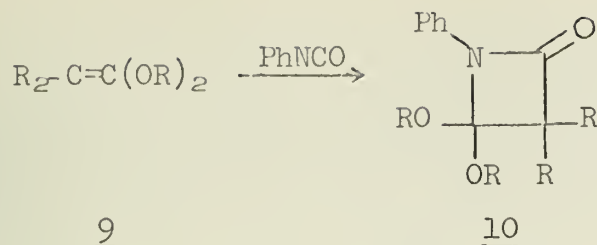
(7) and phenyl isocyanate, an 84% yield of 3,3-dimethyl-1-phenyl-4-pyrrolidino-2-azetidinone (8) was obtained. Corresponding morpholino- and piperidinyl-olefins were also



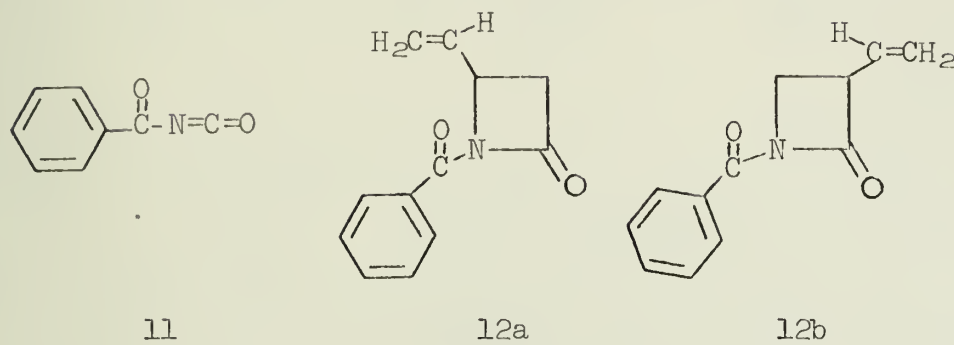
successfully used.

Scarpatti and his co-workers found that disubstituted ketene acetals (9) and phenyl isocyanate react to give the cycloadducts 10, while monosubstituted ketene acetals give linear adducts.<sup>4-6</sup>





was shown to be 12a rather than 12b by cleavage to the free  $\beta$ -amino acid followed by

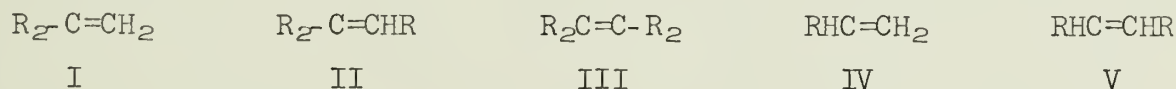
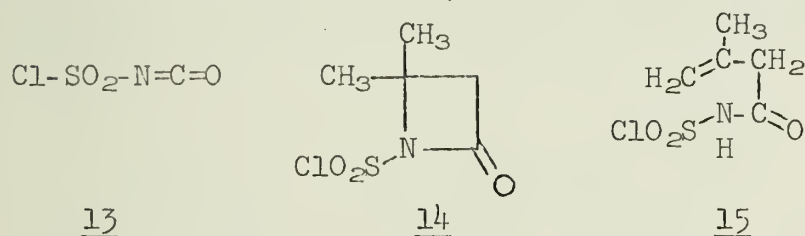


Benzoyl isocyanate has been found to undergo addition to 1,3-dienes to give  $\beta$ -lactam products.<sup>7</sup> Butadiene and benzoyl isocyanate (11) react to give N-benzoyl-4-vinyl-2 azetidinone (12a). The product

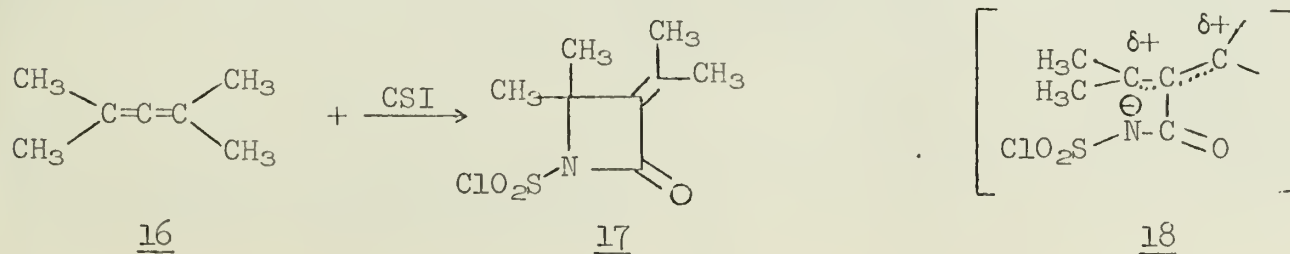
heating to lose ammonia, and then addition of bromine to give 2,3,4,5-tetrabromovaleric acid, a known compound. Benzoyl isocyanate has been found to react analogously by 1,2-cycloaddition to alkenes,<sup>8</sup> p-benzoquinone,<sup>9</sup> and  $\alpha$ -naphthoquinone.<sup>9</sup>

sulfonyl isocyanates was first established by Graf.<sup>10,11</sup> He found that while chlorophosphonyl isocyanate, tosyl isocyanate, phenyl isocyanate, and other simple isocyanates would not react with olefins, if he used the more strongly electron-withdrawing chlorosulfonyl isocyanate, reaction would occur to give  $\beta$ -lactams and unsaturated amides. Isobutylene and chlorosulfonyl isocyanate (13) react to give the  $\beta$ -lactam 14 (70%) and the unsaturated amide (15) (30%). The substitution pattern of the aliphatic olefin influenced the rate of the

reaction, the rate decreasing in the sequence I  $\rightarrow$  V.

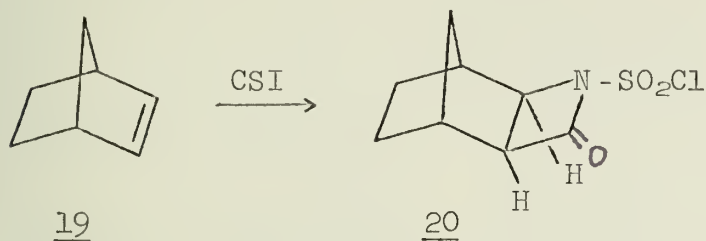


Considerable work with chlorosulfonyl isocyanate (CSI) has been done by Moriconi and his coworkers. The reactions of chlorosulfonyl isocyanate with olefins,<sup>12</sup> allenes,<sup>13</sup> conjugated dienes,<sup>14</sup> cyclopropanes,<sup>15</sup> and strained systems such as norbornene and norbornadiene<sup>16</sup> have been studied. In each case Moriconi found that  $\beta$ -lactam products were isolable with suitable control of reaction conditions. Addition of CSI to allene (16) gave 1-chlorosulfonyl-4,4-dimethyl-3-isopropylidene 2-azetidinone (17) in 67% yield. This type of reaction is the first instance of a  $\beta$ -lactam with an exocyclic double bond. A mechanism involving an allyl-type stabilized carbonium ion (18)





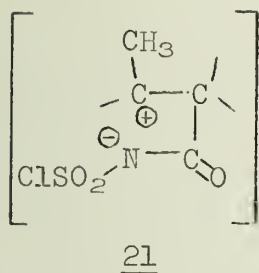
is postulated. In order to test the possible validity of this pathway, Moriconi investigated the addition of CSI to the rearrangement-prone norbornene-type ring systems. The addition of CSI to norbornene (19), norbornadiene, *exo*- and *endo*-dicyclopentadiene, and bicyclo[2.2.2]octene led in each case to high yields of the corresponding N-chlorosulfonyl-*exo*- $\beta$ -lactam, for example, 20. Assignment of the *exo*- configuration was based



largely on nmr evidence, the *endo*- protons showing an AB quartet with  $J = 4-5$  Hz, and fine splitting ( $J = 1$  Hz) due to ~~vibral~~ coupling with the bridge anti proton. No skeletal rearrangements were observed in any of the bicyclo compounds.

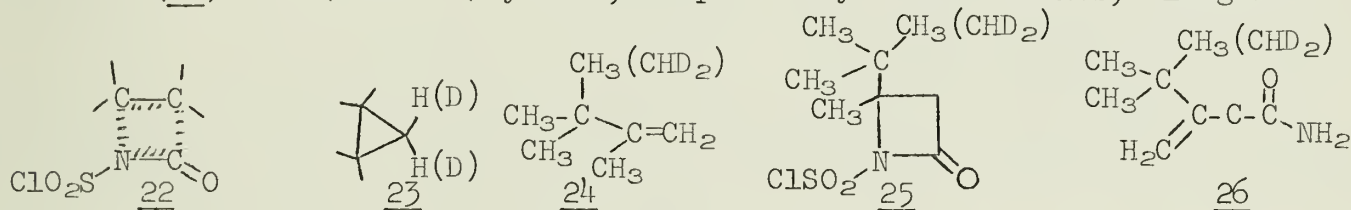
In Graf's pioneering work on the addition of CSI to olefins, he postulated a two-step mechanism involving initial forma-

tion of a 1,4-dipolar adduct (21). Moriconi has found that CSI adds stereospecifically to *cis*- and *trans*- $\beta$ -methylstyrene and *cis*- and *trans*-3-hexene.



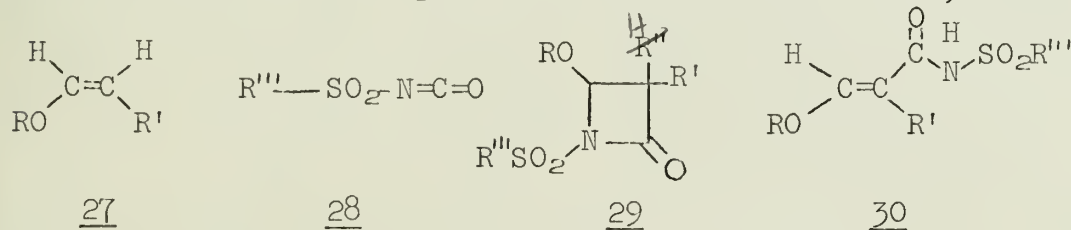
This result eliminates the intermediacy of 21, and suggests three alternative mechanisms: (1) a pseudo-concerted reaction involving partial charge formation, where collapse to the  $\beta$ -lactams occurs faster than rotation; (2) a near-concerted process described by 22; (3) a concerted cycloaddition in which the Woodward-Hoffman rules are applied to heterocumulenic systems such as CSI.

Cyclopropanes react with CSI to give the same  $\beta$ -lactam and unsaturated amide products as are obtained from CSI treatment of the corresponding olefin. For example, the reaction of CSI with 1,1,2,2-tetramethylcyclopropane (23) and 2,3,3-trimethyl-1-butene (24) produced 1-chlorosulfonyl-4-*t*-butyl-4-methyl-2-azetidinone (25) in 65% and 67% yields, respectively, and 4,4-dimethyl-3-methylene-pentamide (26) in 22% and 24% yields, respectively. These results, along with the fact



catalytic amounts of acid converted 23 (unlabelled) into 24, indicated that an olefinic intermediate was involved. Moriconi confirmed by means of deuterium labelling, as indicated, that CSI did indeed catalyze the slow rearrangement to the olefins which then underwent rapid cycloaddition to the  $\beta$ -lactam (23  $\rightarrow$  24  $\rightarrow$  25 + 26).

Effenberger, Gleiter, and Kiefer have formed 2-azetidinones from the reaction of sulfonyl isocyanates (28) with enol ethers (27).<sup>17-19</sup> These workers found that if the reaction were carried out at room temperature or below, the  $\beta$ -lactam (29) was formed in good yield, while if boiling benzene was used, the thermodynamically more stable  $\beta$ -alkoxy-acrylamide (30) was the major product. In addition, if the reaction was stopped at room temperature after a minute or two, almost complete stereospecificity



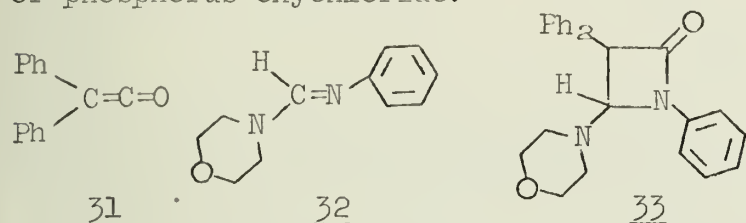
was found, but if it was allowed to run over an hour, an equilibrium mixture of products was obtained. If the isolated  $\beta$ -lactam was refluxed in benzene, or if a mixture of

the two types of products was placed in a strongly polar solvent, complete conversion to the  $\beta$ -alkoxy-acrylamide resulted.



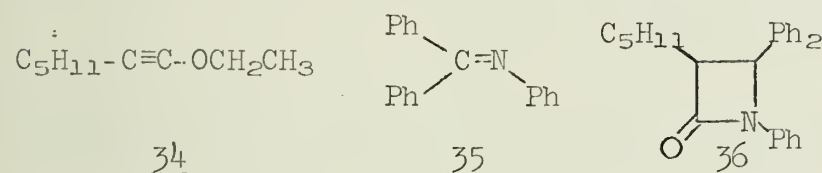
# REACTIONS UTILIZING KETENES, IMINES, AND ACID CHLORIDES

The cycloaddition of diphenylketene to N,N,N'-trisubstituted amidines has been successfully used as a synthesis of  $\beta$ -amino- $\beta$ -lactams.<sup>20</sup> The reaction of diphenylketene (31) and 4-(N-phenylformimidoyl)-morpholine (32) resulted in formation of 1,3,3-triphenyl-4-morpholino-2-azetidinone (33) in about 45% yield. This reaction was carried out on a number of N,N,N'-trisubstituted amidines, and appears to be fairly general, although only aromatic groups were used at the N'-position. The amidines were prepared by reaction of disubstituted amides with primary amines in the presence of phosphorus oxychloride.



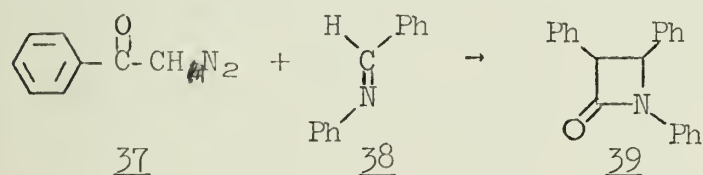
Sheehan and Corey in their review indicated that monosubstituted ketenes (aldoketenes) had not yet been successfully employed in  $\beta$ -lactam synthesis, because they react slowly with imines and show a great tendency to polymerize. In 1959 Van Leusen

and Arens investigated the reaction of what they considered to be aldoketenes, and imines.<sup>21</sup> The suspected aldoketenes were generated by heating 1-ethoxy-1-alkynes to about 130°, with elimination of ethylene. By adding a dilute solution of the ethoxyalkyne in xylene to a refluxing solution of the imine in xylene, they were able to minimize reaction of the aldoketene with starting ethoxyalkyne to give cyclobutenone ethers, and at the same time suppress polymerization. Thus, reaction of ethoxyheptyne (34) with benzophenone-anil (35) in the above manner gave a 70% yield of 3-pentyl-1,4,4-triphenyl-2-azetidinone (36). The only starting materials employed were aromatic imines.



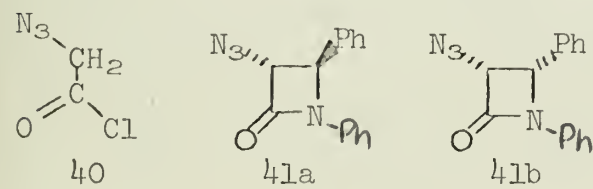
and alkyl-substituted acetylenic ethers, so the generality of the approach has not yet been established. Another method in which aldoketenes are used to form  $\beta$ -lactams is described by Kirmse and Horner.<sup>22</sup> When diazo

ketones are photolyzed, ketenes are the product. If this is done with a Schiff base in the solution, a  $\beta$ -lactam is the product. Irradiation of benzoyldiazomethane (37) and benzalaniline (38) in benzene gave a 74% yield of the  $\beta$ -lactam 1,3,4-triphenyl-2-azetidinone (39). This reaction was found to be most effective with aryl substituents on both the diazoketone and the Schiff base.



A. K. Bose and his coworkers have found that addition of substituted  $\alpha$ -azidoacetyl chlorides across C-N double bonds in the presence of triethylamine will produce  $\beta$ -lactams.<sup>23-27</sup> Benzalaniline (38) and  $\alpha$ -azidoacetyl chloride (40) react in the

presence of triethylamine to give both the *cis* and *trans*- isomers of 3-azido-1,4-diphenyl-2-azetidinone (41). Bose found that the slow addition of  $\alpha$ -azidoacetyl chloride

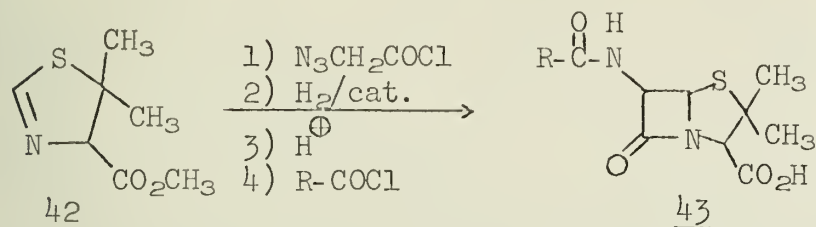


to a solution of benzalaniline and triethylamine in methylene chloride favors the *cis* product [3:1], while addition of triethylamine to the mixture of benzalaniline and  $\alpha$ -azidoacetyl chloride favors the *trans* stereochemistry [3:1]. To examine the cause of this, Bose took each of the pure isomers and heated them with  $\text{CH}_2\text{Cl}_2$  in the presence of

excess triethylamine for several days, and found that no isomerization had taken place. Since the original reactions had been done at room temperature or below, this indicates that the change in the relative proportion of *cis* and *trans* products must be due to steric control of cyclization, rather than equilibration, although just how this occurs is not yet clear. The utility of this reaction comes from the ease with which the azido group can be hydrogenated to an amino group, allowing the  $\beta$ -lactam ring to



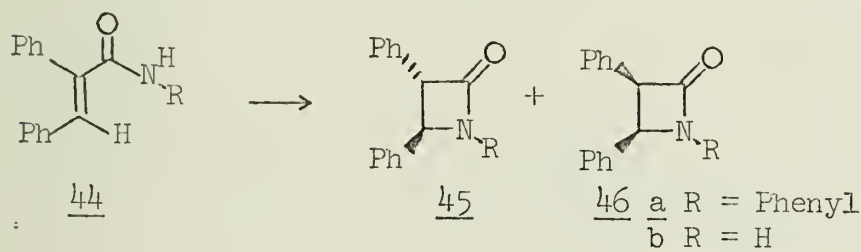
remain intact. Bose has therefore applied this reaction to make a number of penicillin<sup>23, 25, 27</sup> and cephalosporin<sup>26</sup> analogs. Using  $\beta$ -carboxymethyl-5,5-dimethyl-2-thiazoline (42), the corresponding 5,6-trans-penicillin derivatives (43) can be made.<sup>27</sup>



#### PHOTOCHEMICAL METHODS

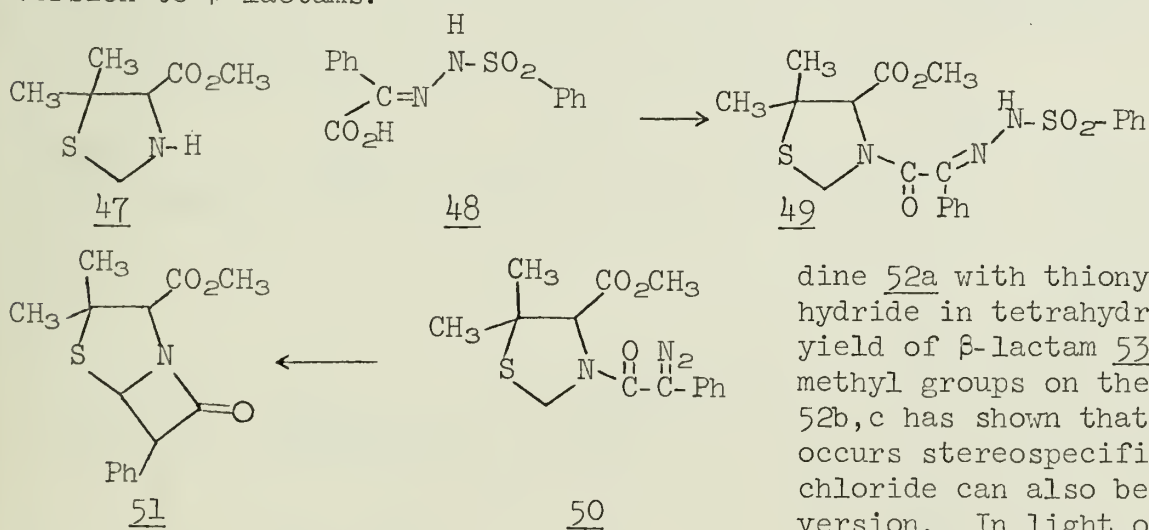
Chapman and Adams<sup>28</sup> have developed a photochemical synthesis of  $\beta$ -lactams. The irradiation of  $\alpha$ -substituted cinnamic and crotonic acids to yield  $\beta$ -lactones suggested to these workers that irradiation

of the corresponding amides would yield either iminolactones or  $\beta$ -lactams. Irradiation of cis- $\alpha$ -phenylcinnamanilide 44a in benzene gave 2.3% trans-1,3,4-triphenyl-2-azetidinone 45a, 37% cis-1,3,4 triphenyl-2-azetidinone 46a, and other products. Irradiation of cis- $\alpha$ -phenyl-cinnamamide 44b in benzene gave a complex mixture from which it was possible to isolate 2.5% trans-stilbene, 13% cis-3,4-diphenyl-2-azetidinone 46b, 3% trans 3,4-diphenyl-2 azetidinone 45b, and 6.2% of an unidentified product.



Corey and Felix<sup>29</sup> have developed what appears to be a general approach to the synthesis of penicillins, in which the key step is cyclization of an  $\alpha$ -dialkyl amide to form the  $\beta$ -lactam ring. Acylation of dl-5,5-dimethyl-4-carbomethoxythiazolidine (47) by the benzenesulfonyl hydrazone

of benzoylformic acid (48) was carried out in dicyclohexylcarbodiimide to give the ester amide 49. Reaction of 49 with one equivalent of sodium hydride produced the  $\alpha$ -dialkyl amide (50). The  $\alpha$ -dialkyl amide was then cyclized photochemically in  $\text{CH}_2\text{Cl}_2$  give methyl 6-phenylpenicillanate (51) as the major product. The  $\alpha$ -dialkyl amide approach can also be used for other structures containing a  $\beta$ -lactam unit. Corey reports that the  $\alpha$ -dialkyl amides considered in his article also undergo thermal conversion to  $\beta$ -lactams.



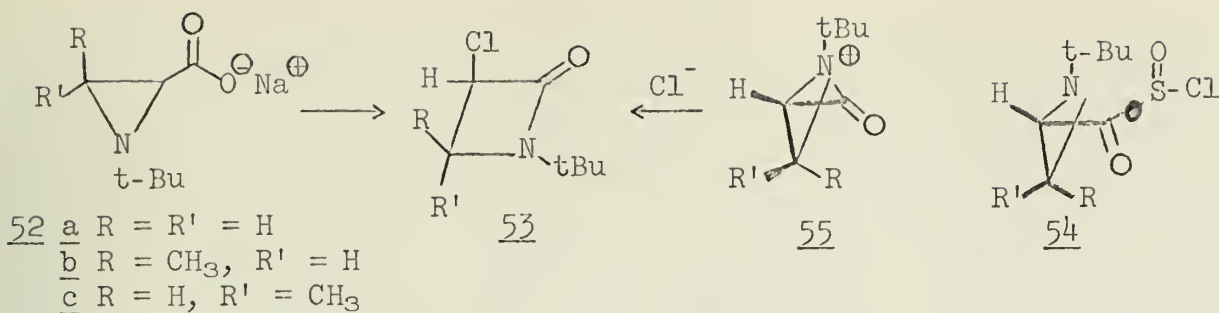
#### RING EXPANSION REACTIONS

The only known reaction of this type has been recently reported by Deyrup.<sup>30</sup> Reaction of aziri-

dine 52a with thionyl chloride and sodium hydride in tetrahydrofuran gave a 33% yield of  $\beta$ -lactam 53a. Substitution of methyl groups on the aziridine ring 52b,c has shown that the reaction occurs stereospecifically. Oxalyl chloride can also be used for this conversion. In light of these facts, this ring expansion is best explained

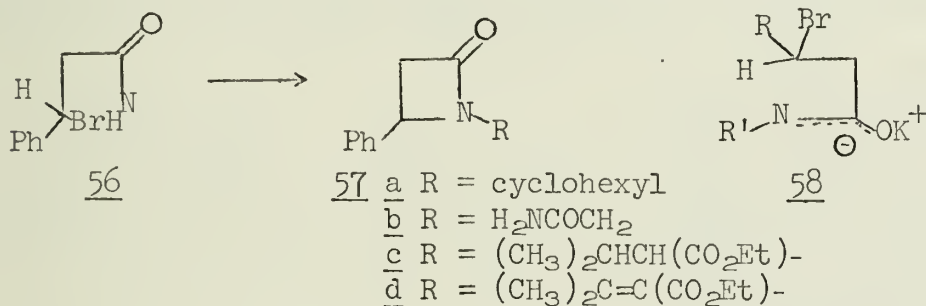
mechanistically in terms of formation of 54 and 55, followed by attack of chloride ion to give the final product.





# INTRAMOLECULAR CYCLIZATIONS

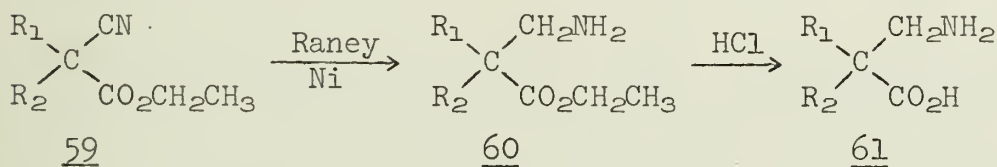
Amides of  $\beta$ -halocarboxylic acids undergo cyclization to  $\beta$ -lactams in yields of 75-85% when shaken in  $\text{KNH}_2$  or  $\text{NaNH}_2$  in liquid ammonia.<sup>31</sup> In this manner  $\beta$ -lactams 57a-d were prepared from the corresponding amides 56. The major side reaction is formation of the unsaturated amides. Alternatively this reaction can be carried out under the action of powdered  $\text{KOH}$  in acetone. The proposed mechanism of the reaction involves the intermediacy of an imide salt 58, which cyclizes to liberate bromide ion.<sup>32</sup> This synthesis has been extended to include 3,3-diphenyl-2-azetidinones.<sup>33</sup>



The synthesis of 2-azetidinones by means of cyclization of a  $\beta$ -aminoester with a Grignard reagent has been extended by Testa and coworkers to include the previously unstudied  $\alpha,\alpha$ -disubstituted  $\beta$ -amino esters (60).<sup>34,35,36</sup> The  $\beta$ -lactams resulting

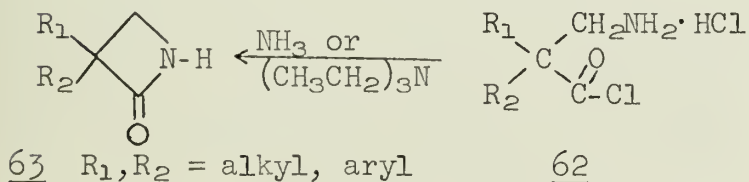
from this synthesis have been found to have a sedative effect on the nervous system, lending greater importance to their synthesis. This type of synthesis has been carried out previously and will not be covered here.

3,3-Disubstituted-2-azetidinones (63) can also be formed starting from ethyl  $\alpha,\alpha$ -disubstituted  $\alpha$ -cyanoacetates 59.<sup>37,38</sup> The key intermediate in this synthesis is the  $\alpha,\alpha$ -disubstituted  $\beta$ -amino propionyl chloride hydrochloride 62, which is obtained by hydrogenation of 59 with Raney nickel followed by hydrolysis to the free acid 61, and treatment with  $\text{PCl}_5$  and acetyl chloride. Cyclization to the corresponding  $\beta$ -lactam is accomplished with either ammonia or triethylamine.

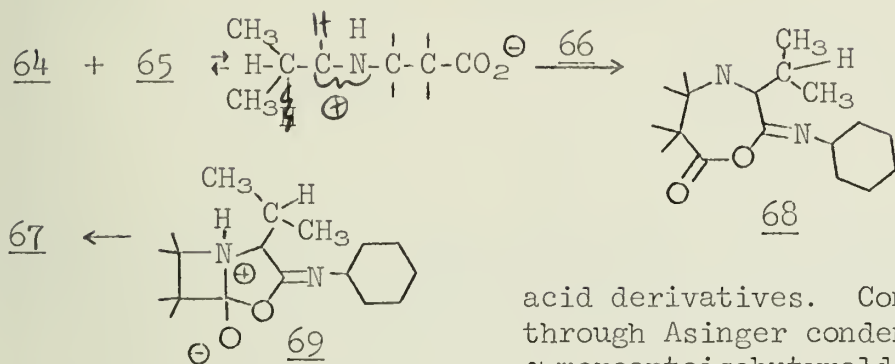
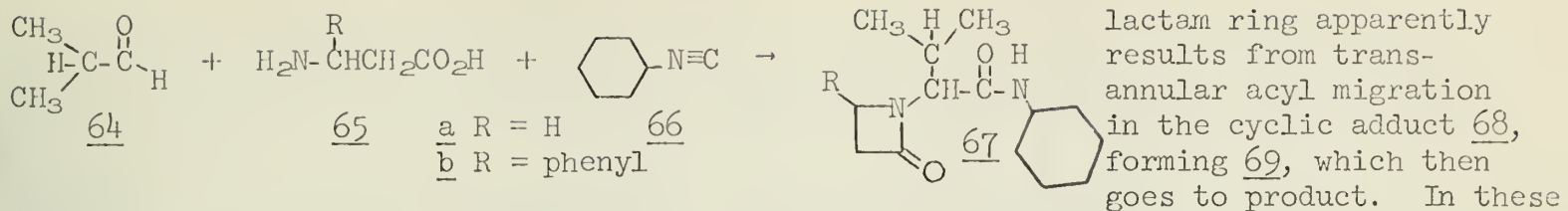


A rather unique synthesis of  $\beta$ -lactams has been carried out by Ugi in connection with his studies on isonitriles.<sup>39</sup>

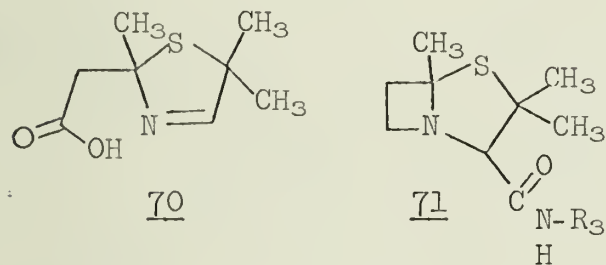
When an isonitrile reacts with a  $\beta$ -amino acid and an aldehyde or ketone, the product is an N-substituted  $\beta$ -lactam in good yield. For example, from  $\beta$ -alanine (64a) or  $\beta$ -phenyl- $\beta$ -alanine (64b) isobutyraldehyde (65), and cyclohexyl isocyanide (66), compounds 67a,b are obtained in good yield. Formation of the  $\beta$ -



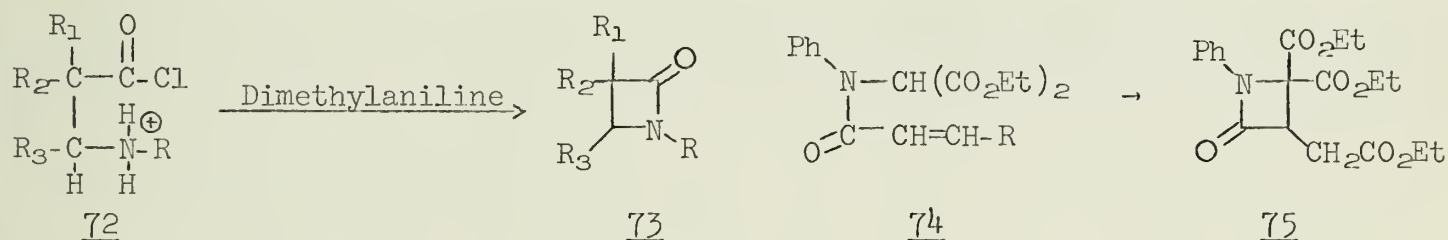




reactions the  $\beta$ -amino acid has simultaneously the function of both an amine and an acid. In demonstrating the versatility of this  $\alpha$ -addition of ammonium ions and anions to isonitriles, Ugi has applied this approach to the synthesis of penicillanic acid derivatives. Compound 70, readily obtainable through Asinger condensation<sup>40</sup> of ethyl acetoacetate,  $\alpha$ -mercaptoisobutyraldehyde, and ammonia, with subsequent hydrolysis of the ester, reacts smoothly with isonitriles to form 5-methyl penicillanic alkylamides (71). Similarly, 6-methyl penicillanic acid amides may be obtained from the corresponding starting materials.

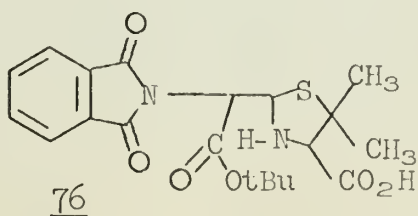


By the addition of amines to atropic acid, Blicke and Gound<sup>41</sup> were able to prepare a number of  $\beta$ -amino acids, which they then converted to acid chloride hydrochlorides (72) by the action of ethereal HCl and thionyl chloride. Interaction of these compounds 72 with dimethylaniline in benzene gave the corresponding 2-azetidinones (73) in 61-92% yield. Diazomethane was also used to carry out this reaction, but yields were smaller.



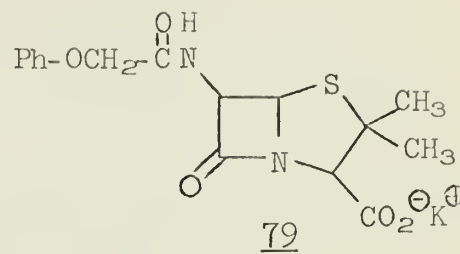
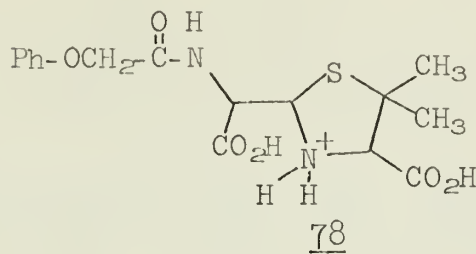
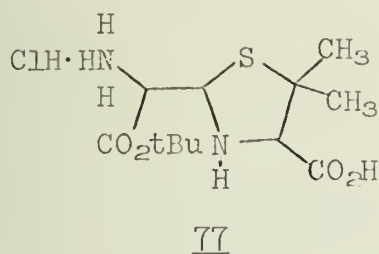
$\beta$ -Lactams (75) can be synthesized by means of an intramolecular Michael reaction utilizing substituted acrylamides (74), with piperidine as the base.<sup>42</sup> This method works only when R is fairly strongly electron-withdrawing (R = CO<sub>2</sub>Et, C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>(p), C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>(o)), since Michael-type cyclization does not occur under the influence of the amide carbonyl. A further limitation is the necessity of the carboxylic acid functions at the 4-position of the product.

The major work in the field of the total synthesis of penicillins has been done by Sheehan and his coworkers.<sup>43-49</sup> During this work a new method of cyclization to  $\beta$ -lactams has been described. Though this work is not covered in the Sheehan and Corey review article, it has been reviewed several times since then<sup>50,51</sup> and therefore will be examined only briefly. The first total synthesis of a natural penicillin (penicillin V, phenoxymethylpenicillin) was achieved in 1957 by a new method of cyclization. D-76 was treated with hydrazine followed by hydrochloric acid to give the amine hydrochloride 77, which was acylated with phenoxyacetyl chloride and treated with anhydrous HCl to remove the *t*-butyl group, to give D- $\alpha$ -phenoxymethyl-



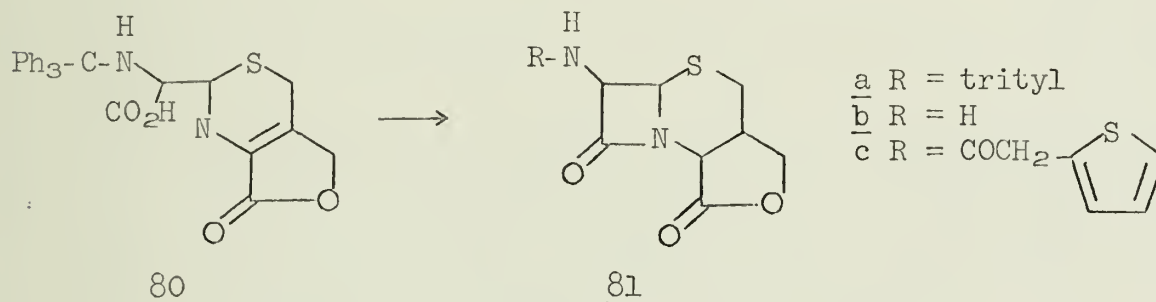


penicilloic acid (78). Cyclization of this compound was achieved in 10-12% yield by treatment with N,N'-dicyclohexylcarbodiimide to yield totally synthetic penicillin V (79), isolated as its potassium salt. N,N'-diisopropylcarbodiimide has also been

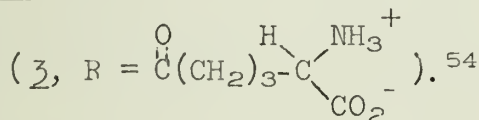


used successfully for this cyclization. Utilization of the trityl group to protect the 6-position during cyclization, followed by detritylation with dilute hydrochloric acid, allows the formation of 6-aminopenicillanic acid, the key intermediate in the synthesis of both natural and synthetic penicillins.

Dicyclohexylcarbodiimide has also been successfully utilized to synthesize a compound in the cephalosporin series, d,l-6,7-trans-cephalothin-lactone (81c).<sup>52</sup> Ring closure of the N-trityl derivative 80 to give 81a followed by detritylation (81b) and acylation gave the desired racemic derivative 81c.



Perhaps the most elegant method was applied by Woodward in the total synthesis of cephalosporin C,<sup>53</sup> in which triisobutylaluminum in toluene was used to convert a cis-amino ester into a  $\beta$ -lactam, which was eventually transformed into cephalosporin C



## SUMMARY

Numerous methods have been devised toward the synthesis of  $\beta$ -lactams. Some of these are fairly general. Most, however, are limited in some respect, which makes them of somewhat less synthetic utility. Methods now exist, however, for the synthesis of  $\beta$ -lactams with a wide variety of substitution patterns in fair yield. Progress in the future needs to be directed toward increasing the generality and yield in syntheses of this strained ring system.

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# UNUSUAL SOLVOLYTIC BEHAVIOR IN TRIFLUOROACETIC ACID

Reported by Bruce R. Harris

September 29, 1969

## INTRODUCTION

The intention of this seminar is to review the most pronounced features in solvolytic reactions conducted in trifluoroacetic acid. Although the primary concern here will be on the special effects observed in this solvent, many unique aspects are seen to stand out best when comparisons are made with other solvents. One such comparison, involving solvent polarities, is indicated for several solvents by the data in Table I. The log  $k_1$  and  $Y$  values, being measures of solvent ionizing power, indicate that trifluoroacetic acid is the most highly ionizing medium of those listed. This interesting behavior, as well as the acid's low nucleophilicity, is called upon to explain the results of a number of studies which follow.

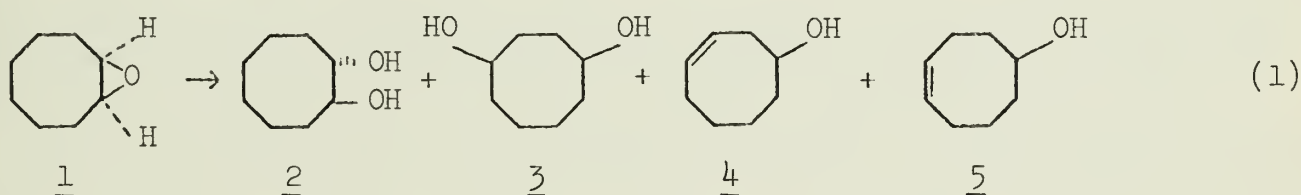
Table I. Quantitative Measures of Solvent Polarity

Solvent	$D^a$	$\log k_{\text{neophyl}}(75^\circ)^c$	$\log k_1(75^\circ)^d$	$Z^f$	$Y^h$
$C_2H_5OH$	24.3	-5.28	-3.20	79.6	-2.033
$CH_3CO_2H$	6.2	-4.70	-2.77	79.2	-1.639
$HCO_2H$	58	-2.52	-0.93	96.7 <sup>g</sup>	2.05 <sup>4</sup>
$CF_3CO_2H$	8.42 <sup>b</sup>	1.05	-0.10 <sup>e</sup>	103.4 <sup>g</sup>	3.60 <sup>i</sup>

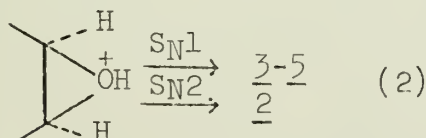
<sup>a</sup>Dielectric constants, data from ref 1. <sup>b</sup>Ref 2. <sup>c</sup>Rates of solvolysis of 2-methyl-2-phenyl propyl tosylate from ref 3. <sup>d</sup>Rates of solvolysis of 2-methyl-2-p-anisyl propyl tosylate from ref 4. <sup>e</sup>Extrapolated value from plot of  $\log k_{\text{neophyl}}$  vs.  $\log k_1$ . <sup>f</sup>Transition energies for charge transfer band of 1-ethyl-4-carbomethoxypyridinium iodide, data from ref 5. <sup>g</sup>Calculated from the equation of the least squares line from ref 4,  $Z = 104.2 + 8.11 \log k_1$ . <sup>h</sup>Ref 6. <sup>i</sup>Extrapolated value from plot of  $Y$  vs.  $Z$ .

## PROXIMITY EFFECTS

Cope<sup>7</sup> has studied the extent to which transannular reactions occur in the solvolysis of cis-cyclooctene oxide (1) in various acids. The major products, after saponification of esters, are illustrated in equation (1). Products 3-5 are formed by a transannular



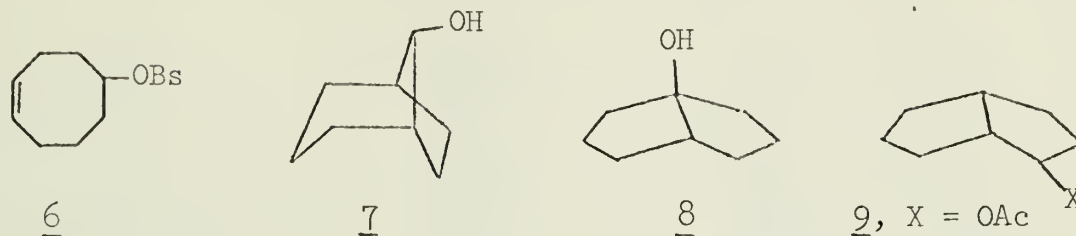
reaction involving a shift of a hydrogen atom in close proximity to the epoxide function across the ring, while 2 is the normal solvolysis product.<sup>7</sup> The products arising from trifluoroacetolysis of 1 are solely 3-5 whereas the buffered acetolysis of 1 leads to 76% 2 and 24% transannular products.<sup>7</sup> The difference in products can be explained by having protonated (1) undergoing competing  $S_N1$  and  $S_N2$  pathways (equation 2), the former being characteristic of the medium of highest ionizing power and the latter characteristic of the medium of greatest nucleophilicity.



These same workers<sup>8</sup> have also found that the trifluoroacetolysis of brosylate (6) results (after hydrolysis) in products containing among others 31% of the carbon shift product (7) and 12% of the hydrogen shift product (8).<sup>8</sup>



On the other hand, buffered acetolysis of 6 gives 35% total of exo (32%) and endo (48%) acetates (9), plus the acetate corresponding to 6 and also elimination products.<sup>9</sup> Again, the results obtained in trifluoroacetic acid can be explained in terms of its high ionizing power and low nucleophilicity.



Peterson<sup>10</sup> has examined hydride shifts in acyclic systems. Some results are summarized in Table II. The interesting features of the reactions in trifluoroacetic acid are the rapid rates of tosylate solvolyses and the large percentage of rearrangement of the substitution products, reflecting the low nucleophilicity of this solvent.

Table II. Rates and Percentage Substitution for Tosylate Solvolyses<sup>a</sup>

Reactant	Solvent	k X 10 <sup>4</sup> , sec <sup>-1</sup> , 25°	Substitution, %
2-Hexyl tosylate	CF <sub>3</sub> CO <sub>2</sub> H	2.2 ± 0.2 <sup>b</sup>	13.5 ± 2 (78% 2-hexyl, 22% 3-hexyl)
2-Hexyl tosylate	CH <sub>3</sub> CO <sub>2</sub> H	too slow to measure	86.5 ± 2 (98% 2-hexyl, 2% 3-hexyl)
2-Hexyl tosylate	HCO <sub>2</sub> H	0.55	80 ± 2 (94% 2-hexyl, 6% 3-hexyl)
3-Hexyl tosylate	CF <sub>3</sub> CO <sub>2</sub> H	7.5 ± 0.8 <sup>b</sup>	16 ± 2 (19% 2-hexyl, 81% 3-hexyl)

<sup>a</sup>Ref 10. <sup>b</sup>Determined with added bromine.

Also the trifluoroacetolysis of 2-hexyl tosylate is about four times as fast as the formolysis, indicating a difference in ionizing abilities of the two media.

#### INDUCTIVE AND PARTICIPATION EFFECTS

The inductive and participation effects of substituents and the attenuation of the inductive effect with distance have been studied by Peterson<sup>11</sup> through the solvolyses of ω-halo-substituted 2-alkyl tosylates. Values of the ratios of the rate constants for solvolysis of the unsubstituted and substituted tosylates,  $k_H/k_X$ , were determined as were the attenuation factors,  $\epsilon$ , of the inductive effect per methylene group.<sup>11</sup> Also, values of the ratios of the rate constants for halogen assisted and solvent assisted ionization,  $k_A/k_S$ , were derived by determining the deviations of points from the straight line plot of  $\log(\log k_H - \log k_X)$  against the number of carbon atoms in the aliphatic chain.<sup>11</sup> The  $k_S$  values were assumed to lie on the straight line whose slope was  $\log \epsilon$ .<sup>11</sup> Table III summarizes the data, along with data from other related studies.<sup>12-14</sup> Several instructive features are seen from the results. First, in those substrates (4-halo-2-butyl) where halogen participation is not favored, the rate-retarding inductive effect,  $k_H/k_X$ , is greatest in trifluoroacetic acid. This behavior is expected because of its weak solvation of the developing cationic center.<sup>11</sup> Second, the trend in  $\epsilon$  values for the ω-halo tosylates indicates that in the weakly solvating trifluoroacetic acid the carbonium ion charge is more effectively moved, by some mechanism which Peterson<sup>11</sup> suggests to involve hyperconjugative delocalization, closer to the halogen substituent as the chain is successively lengthened.<sup>11</sup> That the  $\epsilon$  values for entry 11 are



Table III. Results for  $\omega$ -Substituted-2-alkyl Tosylates<sup>a</sup> and Related Compounds

Substrate	Quantity	Solvent		
		CF <sub>3</sub> CO <sub>2</sub> H	HCO <sub>2</sub> H	CH <sub>3</sub> CO <sub>2</sub> H
1. 4-chloro-2-butyl	$k_H/k_X$	329	129	18.7
2. 5-chloro-2-pentyl	$k_H/k_X$	1.06	3.43	1.69
	$k_\Delta/k_S$	33	3.6	0.7
3. 6-chloro-2-hexyl	$k_H/k_X$	4.32	2.76	1.42
	$k_\Delta/k_S$	1.1	0.7	0.0
4. 7-chloro-2-heptyl	$k_H/k_X$	3.88	2.32	1.13
5. <u>erythro</u> -5-chloro-2-hexyl	$k_H/k_X$	0.362	2.11	1.60
	$k_\Delta/k_S$	99	6.7	0.8
	% ret	92	61	29
6. <u>threo</u> -5-chloro-2-hexyl	$k_H/k_X$	0.545	3.18	
	$k_\Delta/k_S$	65	4.1	
	% ret	89	49	22
7. 4-fluoro-2-butyl	$k_H/k_X$	299	68.2	16.5
8. 5-fluoro-2-pentyl	$k_H/k_X$	8.83	5.04	2.71
	$k_\Delta/k_S$	2.4	0.5	0.2
9. $\omega$ -chloro	$\epsilon$	0.62	0.56	0.35
10. $\omega$ -fluoro	$\epsilon$	0.60	0.48	0.4
11. Unbranched secondary alkyl <sup>b</sup>	$\epsilon$	0.13	~0	~0
12. Unbranched secondary alkyl <sup>b</sup>	$\rho_I$	-15.7	-7.79	-5.72
13. 4-chloro-2-butyl	$\rho_I$	-5.36	-4.49	-2.71
14. 4-chloro-1-pentyl <sup>c</sup>	% Hal shift	99.5	67	27
15. 5-chloro-1-hexyl <sup>c</sup>	% Hal shift	93		
16. 5-bromo-1-hexyl <sup>c</sup>	% Hal shift	95 <sup>+</sup>		

<sup>a</sup>Substrates 1-10 and 13, data from ref 11. Trifluoroacetolyses and formolyses conducted at 25.0°, acetolyses at 70.0°. <sup>b</sup>Non-halogenated tosylates, ref 12. Acetic acid data from ref 13, all temperatures the same as in (a). <sup>c</sup>p-Nitrobenzenesulfonates from ref 14.

considerably smaller than those for entry 9 reflects the rapid attenuation of inductive effects, also effects upon hyperconjugation, by alkyl substituents.<sup>12</sup> Third, the  $\rho_I$  values for both entries 12 and 13 suggest that the oxygen atom in trifluoroacetic acid is weakly bound to the cationic transition state, the more negative values for the first-mentioned entry indicating a greater sensitivity to substituent effects of alkyl groups.<sup>11</sup> Fourth, in those tosylates (5-chloro-2-pentyl) where the solvent variation in values of  $k_H/k_X$  does not parallel that for 4-halo-2-butyl, the disparity is reflected in the amount of halogen participation as measured by the  $k_\Delta/k_S$  values. Again, the participation is strongest in the weakly nucleophilic, highly ionizing trifluoroacetic acid. Halogen assistance is further substantiated by the stereochemical results<sup>11</sup> obtained for the 5-chloro-2-hexyl tosylates, the first evidence for 1,4-chlorine participation.<sup>11</sup> Even a small amount of fluorine participation<sup>11,15</sup> is observed for 5-fluoro-2-pentyl tosylate. Additional variation of halogen participation with solvent is also seen for solvolysis of primary p-nitrobenzenesulfonates (nosylates),<sup>14</sup> including the first example of 1,5-halogen shifts in carbonium ion reactions.<sup>14</sup>

#### PHENONIUM IONS

Trifluoroacetic acid has perhaps shown its unique behavior best in reactions showing enhanced phenyl participation. A lengthy account of this phenomenon will not



be given. It is sufficient to briefly mention that Cram<sup>16</sup> has expounded ethylene-phenonium ion intermediates and that these have been challenged by Brown.<sup>17</sup>

Nordlander<sup>18,19</sup> and Winstein<sup>3,20</sup> have provided extensive quantitative data on the solvolyses of 2-phenylethyl and 1-phenyl-2-propyl tosylates. The results are summarized in Table IV. The  $k_{\Delta}$  and  $k_S$  values were generally determined by relating

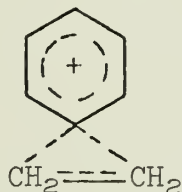
Table IV. Rate Results for 2-Phenylethyl and 1-Phenyl-2-propyl Tosylates

Solvent	$\frac{k(\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{OTs})^a}{k(\text{CH}_3\text{CH}_2\text{OTs})}$	$(k_{\Delta}/k_S)^d$	% rearr	$\frac{k(\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{OTs})\text{CH}_3)}{k(\text{CH}_3\text{CH}(\text{OTs})\text{CH}_3)}$	% ret	$(k_{\Delta}/k_S)^k$
C <sub>2</sub> H <sub>5</sub> OH	0.24 <sup>b</sup>	0.006	0.3 <sup>e</sup>	0.16 <sup>f,g</sup>	7 <sup>g</sup>	0.076
CH <sub>3</sub> CO <sub>2</sub> H	0.37 <sup>b</sup>	1.2	5.5 <sup>e</sup>	0.40 <sup>h</sup>	35 <sup>g</sup>	2.9
HCO <sub>2</sub> H	2.1 <sup>b</sup>	9	45 <sup>e</sup>	0.58 <sup>g,i</sup>	85 <sup>g</sup>	5.6
CF <sub>3</sub> CO <sub>2</sub> H	3040 <sup>c</sup>	23,000	50 <sup>c</sup>	17.1 <sup>j</sup>	100 <sup>j</sup>	5600

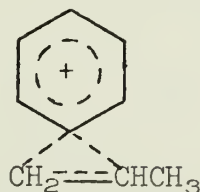
<sup>a</sup>Temp 75°. <sup>b</sup>Ref 21. <sup>c</sup>Ref 18. <sup>d</sup>Data for 2-phenylethyl tosylate, temp 75°, ref 3. <sup>e</sup>Ref 24. <sup>f</sup>Ref 22, temp 50°. <sup>g</sup>Ref 23. <sup>h</sup>Ref 13, temp 70°. <sup>i</sup>Ref 12, temp 25°. <sup>j</sup>Ref 19, temp 25°. When corrected for the phenyl inductive effect the factor for rate enhancement becomes 564. <sup>k</sup>Data for 1-phenyl-2-propyl tosylate, ref 20, temp 50°.

the amount of rearranged labeled product from 2-phenylethyl tosylate<sup>18,24</sup> or product of retained configuration from 1-phenyl-2-propyl tosylate<sup>19,23</sup> to the observed rate constants.<sup>3,20</sup>

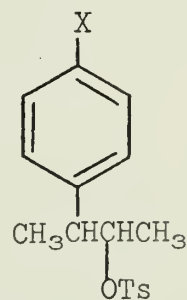
The most prominent feature of the data is the departure of the trifluoroacetolysis rate ratios for phenyl substituted to unsubstituted tosylates from the remaining values. In addition, both phenyl substituted tosylates show a marked tendency to solvolyze in trifluoroacetic acid by way of an anchimerically assisted path,  $k_{\Delta}$ , leading to bridged ions (10) and (11). It is certainly apparent that the ratios  $k_{\Delta}/k_S$  are associated with different responses to solvent nucleophilicity and ionizing power.<sup>3</sup> In fact, the trifluoroacetolysis pathway leading to 11 occurs 99.8%<sup>25</sup> via phenyl assistance. The labeling and stereochemical results in trifluoroacetic acid again build up the case for the formation of 10 and 11, respectively. Also, complete retention (98 ± 3%) of configuration in the trifluoroacetolysis of 2-phenylethyl brosylate has been shown by Snyder<sup>26</sup> using deuterium labeling. To summarize, all these results for trifluoroacetic acid may be understood in terms of a particularly low nucleophilicity<sup>27</sup> and high ionizing power.<sup>4</sup> The latter is probably derived from particularly effective anion solvation through hydrogen bonding.<sup>18</sup>



10



11



12a, X = H  
12b, X = NO<sub>2</sub>

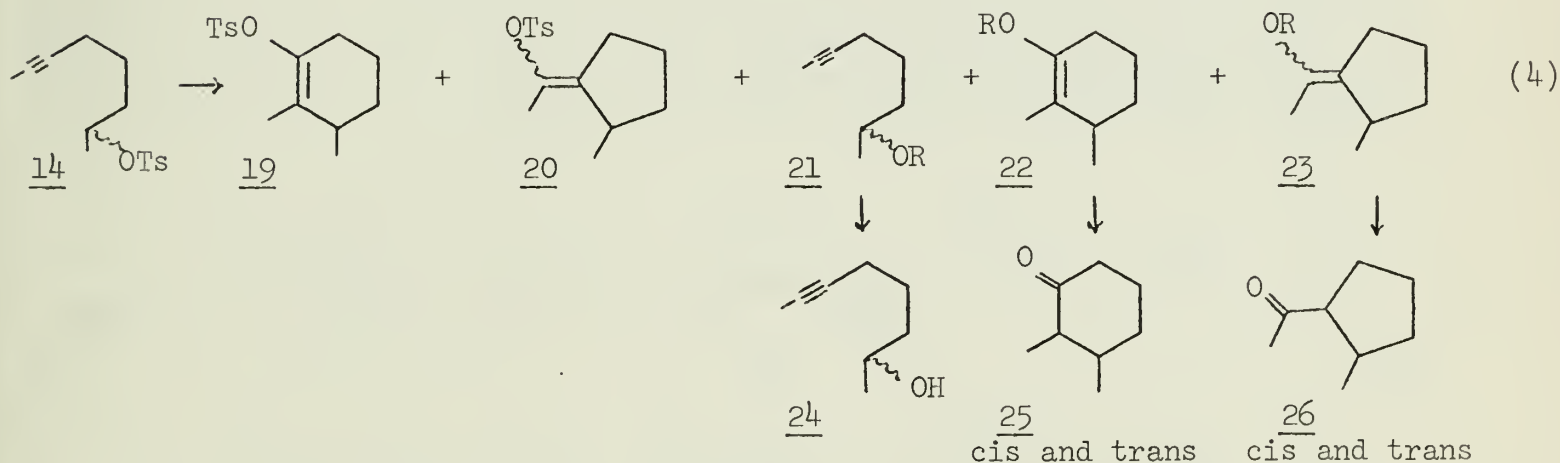
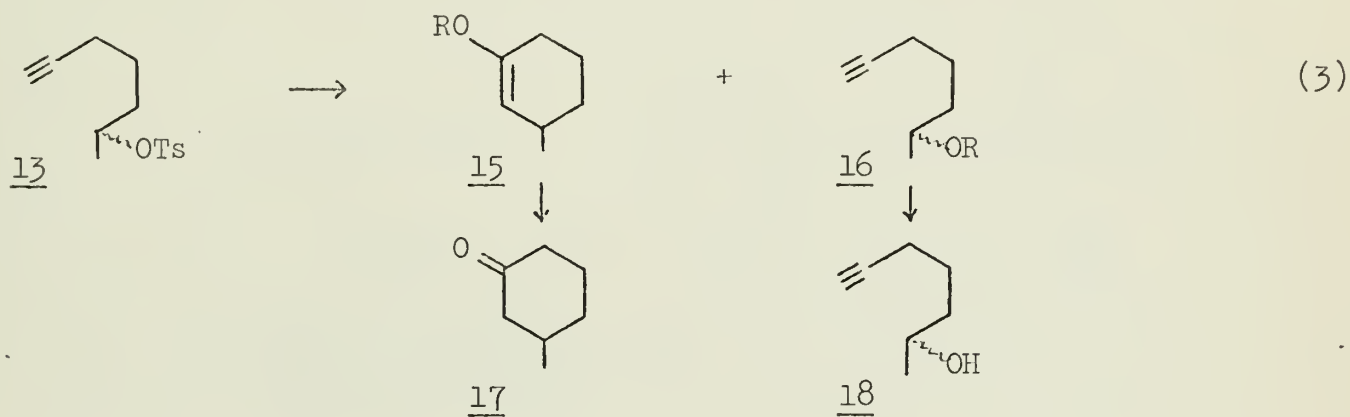
Further support for phenyl participation in trifluoroacetic acid comes from a stereochemical study by Cram<sup>28</sup> involving solvolysis of 3-phenyl-2-butyl tosylate (12a) and its *p*-nitro derivative (12b). The (+)-*threo* isomer of 12b gives ester product which is 95% *threo* whereas the formolysis of L-*threo* (12b) leads to 70% *erythro* ester.<sup>28</sup> Evidently the *p*-nitrophenyl group exerts considerable stereochemical control



over the reaction in trifluoroacetic acid, indicating at least 90% aryl participation. Interestingly, the rate constant ratio for ionization (racemization) of 12a and 12b,  $k^H/k^{NO_2}$ , is 36,000 (8000 when corrected for the *p*-nitrophenyl group inductive effect) for trifluoroacetolysis<sup>28</sup> and 560 for formolysis.<sup>28,29</sup> On the basis of these values one might conclude that the poorly nucleophilic *p*-nitrophenyl group is only weakly participating in trifluoroacetolysis. However, this notion is dispelled by the above-mentioned stereochemical results.<sup>28</sup> Phenonium ions are therefore the principal intermediates in the trifluoroacetolyses of both 12a and 12b.<sup>28</sup>

#### TRIPLE BOND ASSISTANCE

The triple bond<sup>30,31</sup> has also been noted to lend assistance to ionization. Peterson<sup>30</sup> has studied the solvolysis of 6-heptyn-2-yl tosylate (13) and 6-octyn-2-yl tosylate (14) in order to determine the amount of triple bond participation in competition with normal solvolysis. The derived products are shown in equations (3) and (4).



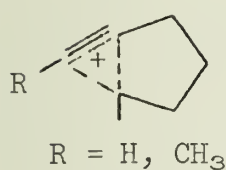
The kinetic results support a participation pathway.<sup>30</sup> The rate constants,  $k$ , are dissected into  $k_\Delta$  and  $k_s$ . The latter are obtained from that of 2-pentyl tosylate<sup>12</sup> by application of a factor which corrects for the inductive effect of the triple bond and then application of the Hammett-Taft equation. Table V summarizes the pertinent kinetic data, where  $k_T$  represents the experimental<sup>30</sup> rate constant. The data indicate that the trifluoroacetolyses of both 13 and 14 occur overwhelmingly via triple bond participation.<sup>30</sup> Also noteworthy is the correspondence between the data in the last two columns, except in the case of the acetolysis data. Here the small magnitude of both inductive and participation effects leads to a relatively large uncertainty in the calculations.<sup>30</sup> To accommodate formation of both five- and six-membered ring products plus rearranged tosylate from trifluoroacetolysis of 14 the intermediate was visualized as 27<sup>30</sup> in order to avoid postulating a high-energy bent vinyl cation.<sup>37</sup>



Table V. Quantities Derived from Rates of Solvolysis; Per Cent Cyclization<sup>a</sup>

Tosylate	Solvent	Rel $k_T$	$k_A/k_S$	100 x ( $k_A/k_T$ )	Cyclization, %
<u>13</u>	CF <sub>3</sub> CO <sub>2</sub> H	10	6.5	87	91
	HCO <sub>2</sub> H	1	0.77	44	40
	CH <sub>3</sub> CO <sub>2</sub> H	1.2	0.073	6.8	27
<u>14</u>	CF <sub>3</sub> CO <sub>2</sub> H	31	84	98.8	100
	HCO <sub>2</sub> H	1.015	5.6	85	78
	CH <sub>3</sub> CO <sub>2</sub> H	1	2.3	70	60

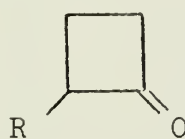
<sup>a</sup>Ref 30. Trifluoroacetolyses and formolyses conducted at 25°, acetolyses at 70°.



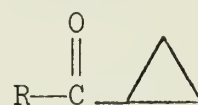
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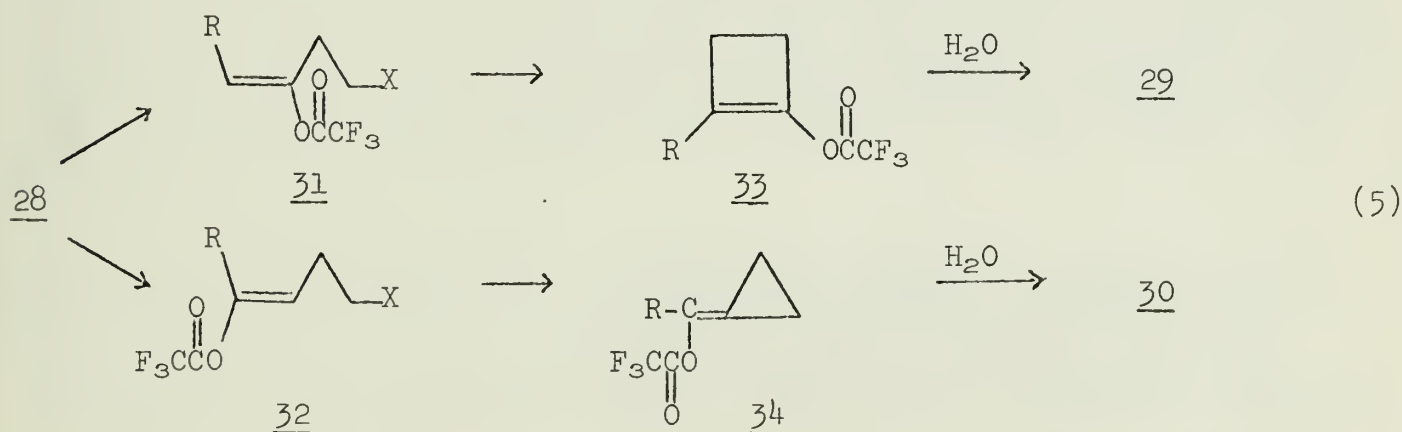
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30

R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, i-C<sub>3</sub>H<sub>7</sub>  
X = OTs, ONs, OSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-*m*-NO<sub>2</sub>,  
OSO<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-3,5(NO<sub>2</sub>)<sub>2</sub>

Triple bond participation of a similar sort<sup>31</sup> has been observed for the trifluoroacetolysis of substituted acetylene derivatives (28) to give products containing greater than 85% (gas chromatographic) of 29.<sup>31c</sup> In the presence of mercuric acetate greater than 75% (gas chromatographic) of 30 is formed.<sup>31c</sup> The mercury salt functions to catalyze the addition of acid to the triple bond as shown in equation (5). Subsequent solvolysis and rearrangement lead to products

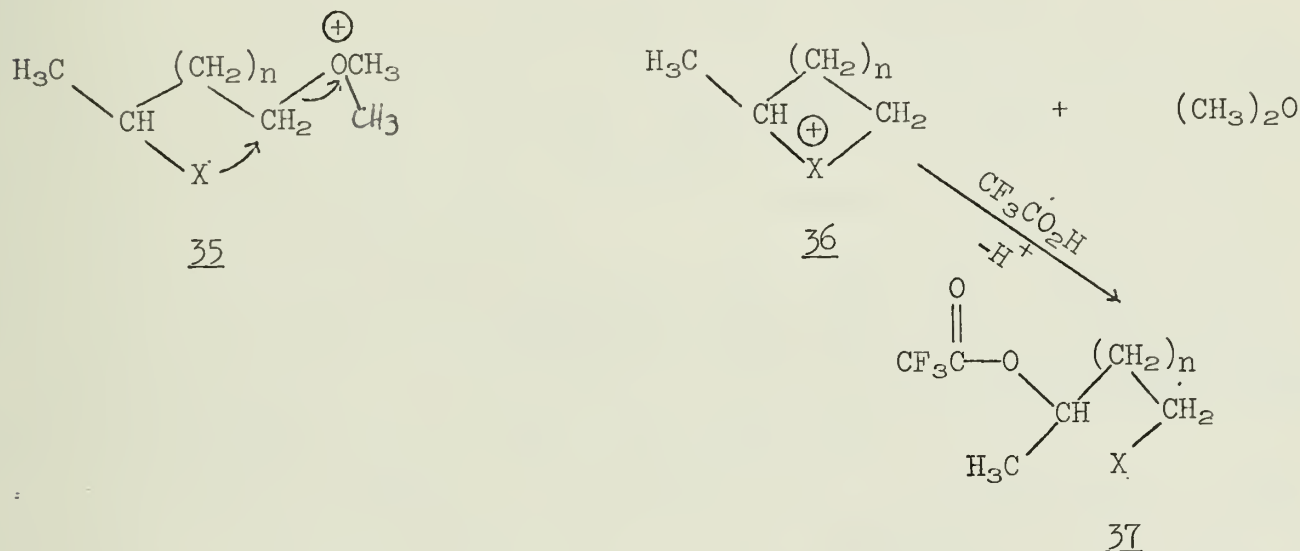


(29) and (30), the latter being the major one.<sup>31c</sup> In the absence of salt no such addition of acid occurs, but rather direct participation by the triple bond is postulated.<sup>31c</sup> In contrast, acetolysis (without mercuric acetate) of 28 gives none of 29 but instead 98% of the acetate corresponding to 28.<sup>31c</sup> The cyclization is therefore favored in the solvent of highest ionizing ability and lowest nucleophilicity.<sup>31c</sup>



A few remaining examples of solvolyses studied in trifluoroacetic acid may be mentioned. Phenyl migration has been observed in the trifluoroacetolysis of medium ring compounds,<sup>32</sup> as have 1,2-hydride shifts.<sup>33</sup>

A halogen shift involving a trialkyloxonium ion intermediate has been postulated by Peterson<sup>34</sup> in the reaction of trimethyloxonium fluoroborate  $(\text{CH}_3)_3\text{O}^+\text{BF}_4^-$  with halo-substituted methyl ethers  $\text{CH}_3\text{CHX}(\text{CH}_2)_n\text{CH}_2\text{OCH}_3$  ( $n=0,2$ ;  $\text{X}=\text{Cl}, \text{Br}, \text{I}$ ) in trifluoroacetic acid. Transient species (35) undergoes an intramolecular displacement of dimethyl ether by halogen to give halonium ion (36) which collapses in an  $\text{S}_{\text{N}}1$ -like manner<sup>34</sup> to form halogen shifted products (37). The oxonium fluoroborate reacts only slowly with the weakly nucleophilic trifluoroacetic acid, unlike acetic and formic acids in which it is rapidly solvolyzed.<sup>34</sup>



Streitwieser<sup>35</sup> has measured secondary deuterium isotope effects in the trifluoroacetolysis of isopropyl tosylate. The isotope effect,  $k_{\text{H}}/k_{\text{D}}$ , for isopropyl- $\alpha$ - $\text{d}$  tosylate is  $1.22 \pm .02$  or  $\Delta\Delta F^\ddagger = 117 \pm 9$  cal/mole.<sup>35</sup> Since the  $\alpha$ -isotope effect for acetolysis of isopropyl brosylate<sup>36</sup> has been determined to be 1.12 or  $\Delta\Delta F^\ddagger = 77$  cal/mole, this comparison suggests that the acetolysis reaction has more nucleophilic solvent participation.<sup>35</sup> The isotope effect in trifluoroacetic acid for isopropyl- $\beta$ - $\text{d}_6$  tosylate is  $2.12 \pm 0.1$  or  $\Delta\Delta F^\ddagger/n = 74 \pm 5$  cal/mole.<sup>35</sup> If this result is compared to the estimated<sup>35</sup>  $\beta$ -deuterium isotope effect of 49 cal/mole for acetolysis of isopropyl tosylate, one may conclude that the transition state for trifluoroacetolysis has greater carbonium ion character than for acetolysis.<sup>35</sup>

## CONCLUSION

There can be no doubt that trifluoroacetic acid shows unusual ionizing ability and low nucleophilicity in solvolytic reactions. Because of its unique solvolyzing ability it has especially made the studies involving phenonium ions more conclusive by providing evidence for long-sought rate enhancements. The future should see new effects being uncovered in reactions involving this acid.

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# THE CHEMISTRY OF CEPHALOSPORIN C ANTIBIOTICS

Reported by Anthony J. Playtis

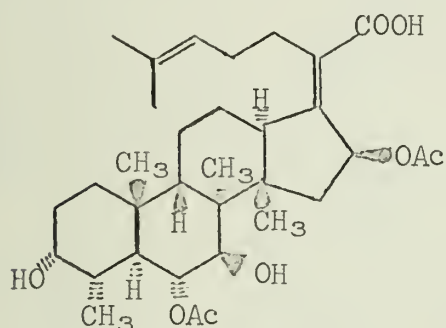
October 2, 1969

## INTRODUCTION

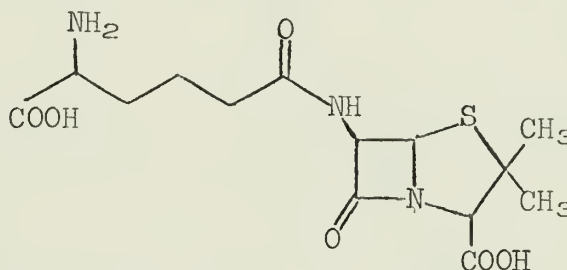
In recent years there has been a great deal of interest in the penicillin related family of antibiotics derived from the natural product cephalosporin C. Although not as potent as the penicillins, the cephalosporins have a broad spectrum of activity, are fairly non-toxic, and are comparatively immune to the  $\beta$ -lactamases produced by penicillin resistant bacteria. The chemistry of these compounds was reviewed by Abraham<sup>1</sup> in 1967. It will be the purpose of this seminar to update and expand upon this review.

## HISTORICAL

In 1948, Brotzu<sup>2</sup> found that a fungus species, Cephalosporium acremonium, isolated from sea water near a sewage outlet on the coast of Sardinia produced a substance which could inhibit the growth of both Gram-positive and Gram-negative bacteria. English workers<sup>3,4</sup> subsequently found that the mold produced several antibiotic substances, which could be roughly classed as either hydrophobic or hydrophilic. The hydrophobic fraction was found to contain five very similar active compounds, which were named cephalosporin P<sub>1-5</sub>. Cephalosporin P<sub>1</sub> was by far the major component, and it was soon found to be a steroid.<sup>5</sup> Although its exact structure is still not completely certain, there seems to be general agreement that formula 1 is correct.<sup>6-8</sup> The hydrophilic fraction was at first thought to have only one component, which was named cephalosporin N. This was correctly assumed to be a penicillin.<sup>9</sup> Degradation studies indicating an unusual D- $\alpha$ -aminoadipoyl side chain led to structure 2.<sup>10</sup>



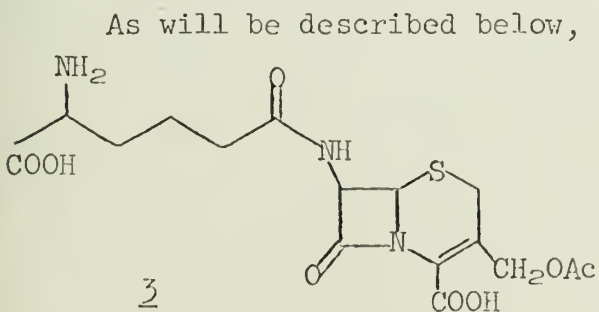
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2

Cephalosporin C was detected<sup>11</sup> as an impurity in cephalosporin N solutions because of its strong uv absorbtion at 260 nm. It was found to be isolable as the dihydrate of its sodium salt by either ion exchange chromatography or by countercurrent distribution techniques.<sup>12</sup>

## STRUCTURE, STEREOCHEMISTRY AND NOMENCLATURE



3

As will be described below, cephalosporin C was shown to have structure 3. The systematic name for cephalosporin C is 3-(acetoxymethyl)-8-oxo-7-(D-5-amino-5-carboxy-n-pentanoylamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.<sup>13</sup> The systematic name and numbering of the ring is not used by the workers in this field, who have adopted a nomenclature for the central ring system which is analogous to that in general use for the penicillins.<sup>14</sup> It is this system, shown in Figure I, which shall be used in this report. X-ray<sup>15,17</sup> and nmr<sup>16</sup> studies have shown the  $\Delta^3$ -cephem system to have conformation 4, with the angle between the two rings somewhat flatter than it is in the penicillins. The  $\Delta^2$ -cephem ring was shown<sup>16,18</sup> by nmr and degradation studies to have the stereochemistry 5, with the C4 hydrogen atom in the beta position.



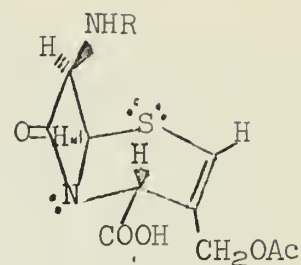
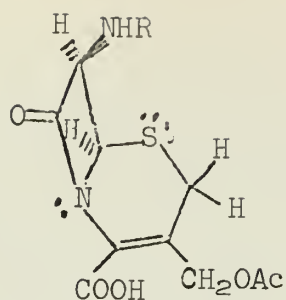
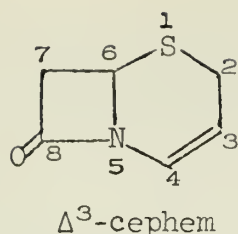
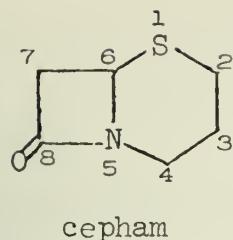
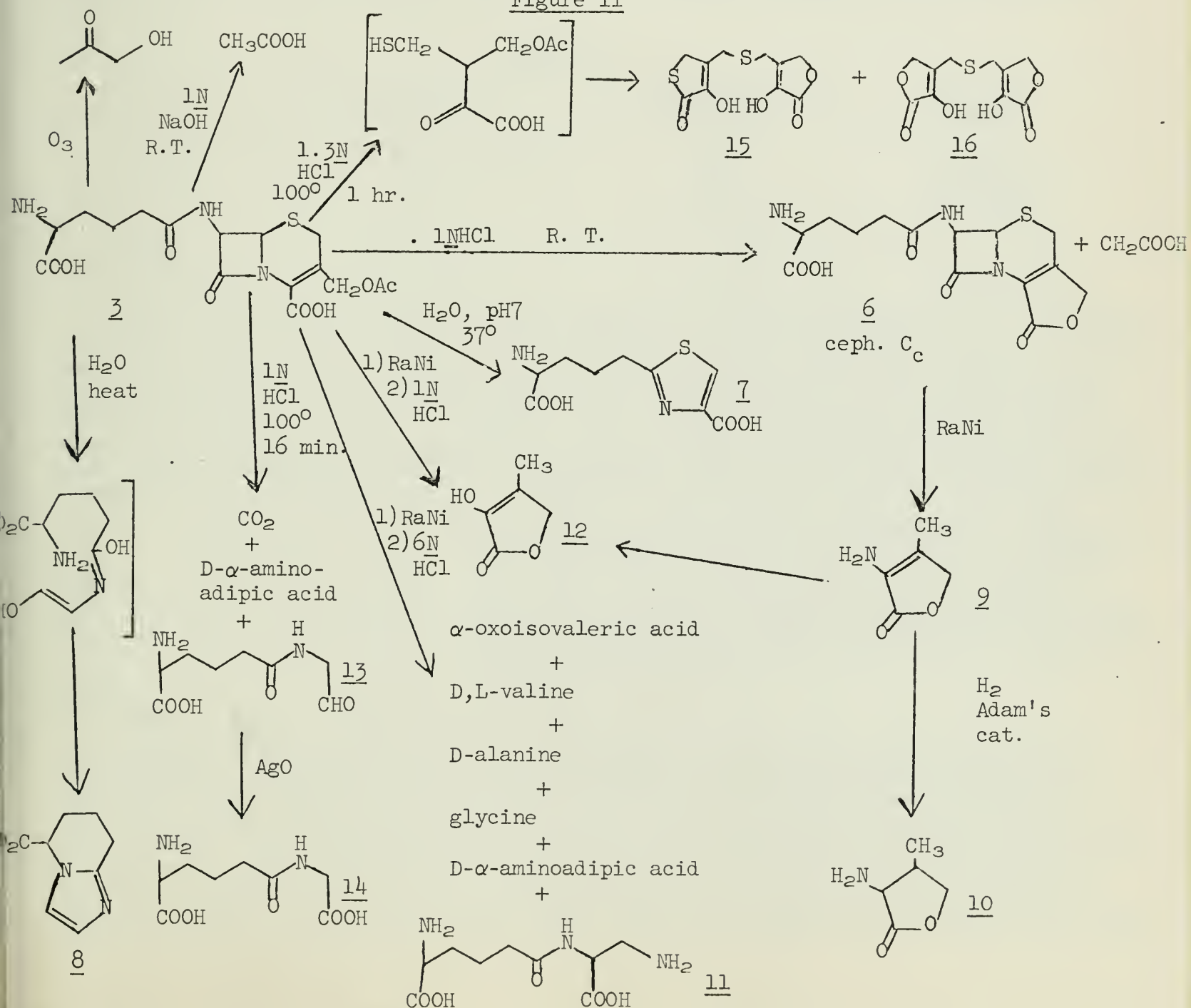


Figure I

## STRUCTURE DETERMINATION

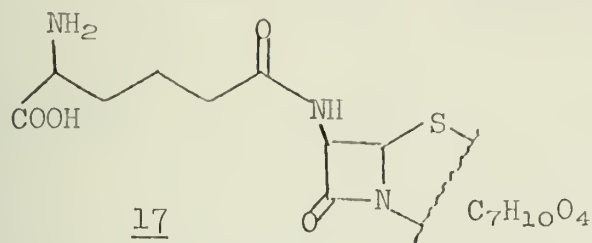
Most of the structural work was done with the sodium salt. A preliminary investigation<sup>11</sup> showed the compound to have a M.W. of  $470 \pm 15$ , and a provisional formula of  $C_{16}H_{20}O_8N_3SNa \cdot 2H_2O$  was assigned. Three titrable groups were present, with  $pK_a$ 's of 9.8, 3.1 and less than 2.6. The molecule was strongly dextrorotatory ( $[\alpha]_D^{20} = +103^\circ$ ), showed uv absorption at 260 nm ( $\epsilon = 9500$ ), and had bands in the infrared at  $5.61 \mu$  and  $5.77 \mu$ , which were thought to be indicative of a  $\beta$ -lactam and an ester respectively. A degradation study was then undertaken;<sup>19-23</sup> this is summarized in Figure II. Several of the

Figure II





degradation products not previously reported (7, 9, 14, 16) were synthesized.<sup>15,20,24-26</sup> The presence of compounds 7, 11, and several products which were also observed during the degradation of cephalosporin N led to the formulation of partial structure 17. The



structure of the  $C_7H_{10}O_4$  fragment of the molecule was deduced from the structures of the cyclic degradation products 9, 10, 12, 15, 16, the formation of acetic acid, and the fact that the isolated valine was racemic. Nmr spectra confirmed this structure and eliminated the possibility of a gem-dimethyl group, as found in the penicillins. The conclusions reached by this degradation study

were almost immediately confirmed by x-ray analysis.<sup>15</sup>

### SPECTROSCOPY

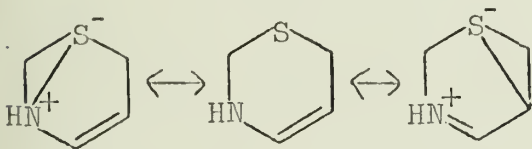
The nmr and infrared spectra of cephalosporins have been reviewed by Green et al.<sup>27,28</sup> The most striking feature of the infrared absorption is the four carbonyl stretching bands between  $1650$  and  $1800\text{ cm}^{-1}$ , corresponding to the acetoxy, carboxy,  $\beta$ -lactam and 7-amido groups. The important nmr signals for the cephalosporins are listed in Table I. In  $D_2O$ , the signal for the 7-proton collapses to a doublet with  $J = 4-5$  cps.

Table I

position	chemical shift (delta)	coupling constant (cps)	type of signal
6-proton	5-6	4-5	doublet
7-proton	5-6	4-5	doublet of
		8-9	doublets
2-protons	3-4	18	AB pattern
3-exo methylene	4.5-5.5	13	AB pattern

The ultraviolet absorption of cephalosporins at about  $260\text{ nm}$  comes at a wavelength much longer than would be expected for an N-acyl  $\alpha,\beta$ -unsaturated amino acid (est.  $220\text{ nm}$ ), and it was suggested that the stereochemistry of the ring system suppressed the normal amide resonance and allowed the nitrogen lone electron pair to exert an auxochromic effect.<sup>21</sup> However, this was shown to be only a partial explanation by Lowe et al.<sup>26</sup> who reported compound 9 to absorb at  $248\text{ nm}$ . These workers suggested that the sulfur atom also causes a bathochromic shift.<sup>29</sup> In agreement with this view, the d-orbital resonance structures shown in Figure III were proposed as contributing to the uv absorption.<sup>30</sup>

Figure III



The mass spectra of two cephalosporin methyl esters has been studied by Richter and Biemann.<sup>31</sup> Because of the large number of heteroatoms, a high resolution instrument is a great help with these compounds. The cephem ring appears to produce a characteristic pattern of peaks, which the authors explain with a number of fragmentation schemes.

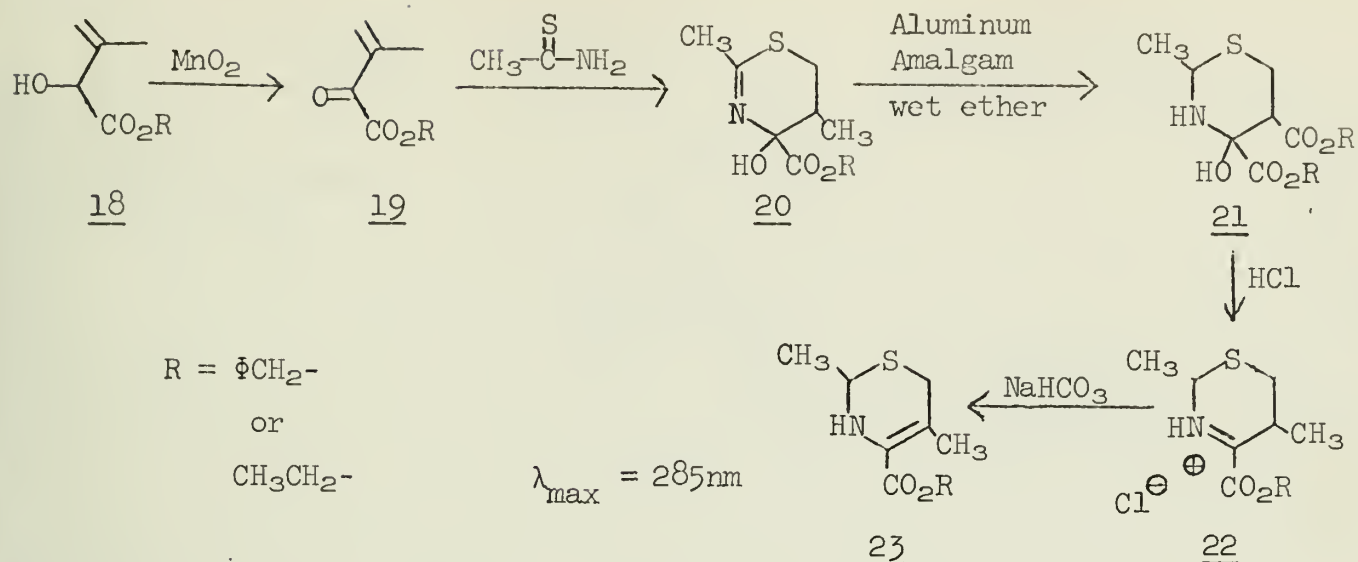
### SYNTHESIS

Because of the obvious structural similarities between the penicillins and the cephalosporins, synthetic routes roughly parallel to Sheehan's classic penicillin synthesis<sup>32</sup> were first considered, even though it was recognized that the weak nucleophilicity of the thiazine ring nitrogen could make closure of the  $\beta$ -lactam difficult.<sup>26,33,34</sup> The 3,6-dihydro-(2H)-1,3-thiazine ring contained in the  $\Delta^3$ -cephem system was previously unknown, and it was first synthesized independently by the groups of Long<sup>30</sup> and Lowe.<sup>35</sup> This synthesis, shown in Figure IV, is a remarkable example of parallel efforts, with the two groups using identical reagents in six consecutive steps.

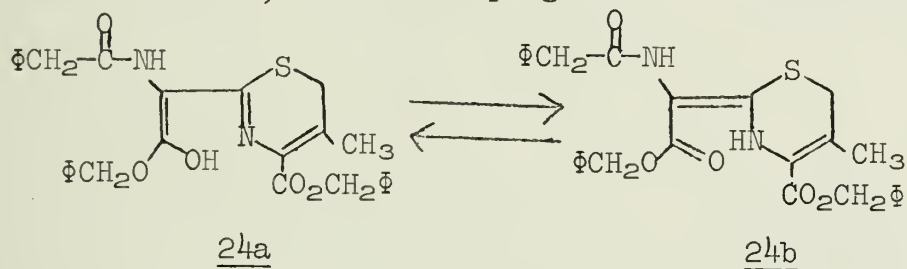


Figure IV

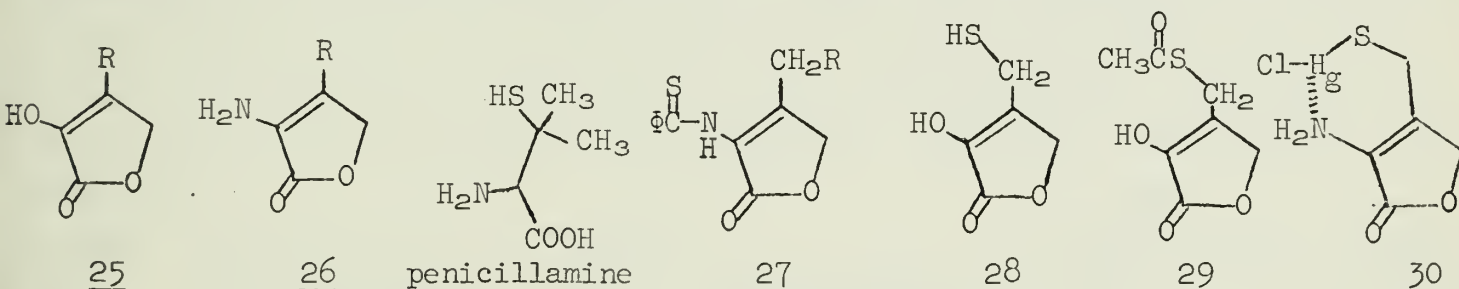
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By condensing an appropriately substituted thioamide with 18, Lowe and co-workers<sup>36</sup> succeeded in synthesizing 24, which appeared to have possibilities as a  $\Delta^3$ -cephem precursor. However, no further progress in this direction was reported.



A large number of synthetic schemes centered around  $\beta$ -substituted  $\alpha$ -tetronic acids 25 and  $\alpha$ -aminobutenolides 26 as starting materials. These compounds could serve as analogs to the penicillamine used in Sheehan's work and presented the added advantages of protecting the groups in the 3 and 4 positions and stabilizing the



location of the thiazine ring double bond.<sup>33</sup> Lowe *et al.*<sup>26</sup> unsuccessfully attempted ring closures with compounds of the type 27, where R- is a good enough leaving group to make the  $\beta$ -methylene susceptible to nucleophilic attack by the sulfur atom. Long and co-workers<sup>30</sup> attempted to condense the free thiol 28 with an aldehyde and ammonia, a type of ring closure reported by Asinger, Theil, *et al.*<sup>37</sup> The failure of this attempt was probably due to the tendency of 28 to condense to the sulphide 16 under even slightly basic conditions. Galantay *et al.*<sup>33</sup> have tried a similar condensation with 29 and were also thwarted by the formation of 16. These workers have prepared 30 as a possible intermediate, but have not reported any further progress. A partial success appears to have been achieved by French workers,<sup>39</sup> who report the synthesis of racemic deacetylcephalothin lactone 35 by the synthetic route shown in Figure V. No experimental details are given for the critical coupling reaction between 28 and 31 which eluded the efforts of previous workers. However, it does appear that basic conditions are avoided. An alternate synthesis developed at the Squibb institute,<sup>39</sup> which avoids the use of the unstable thiol 28, is shown in Figure VI. Further investigations with butenolides have been conducted by Reinhoudt *et al.*,<sup>40-42</sup> but no ring closures have been reported.



Figure V

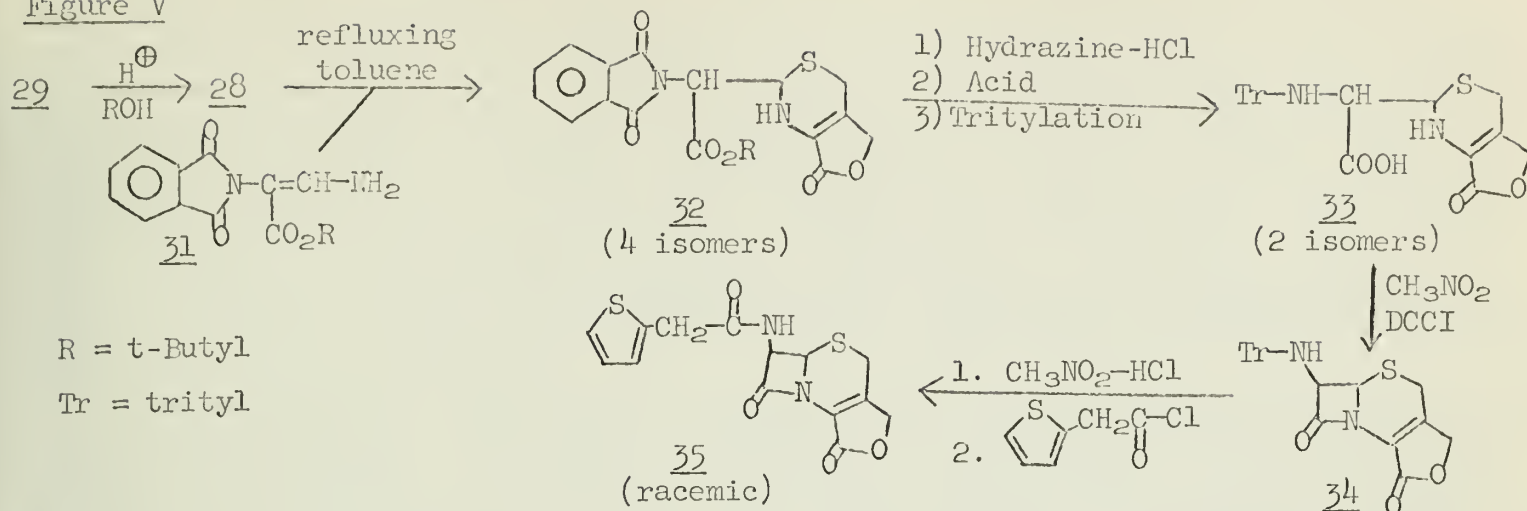
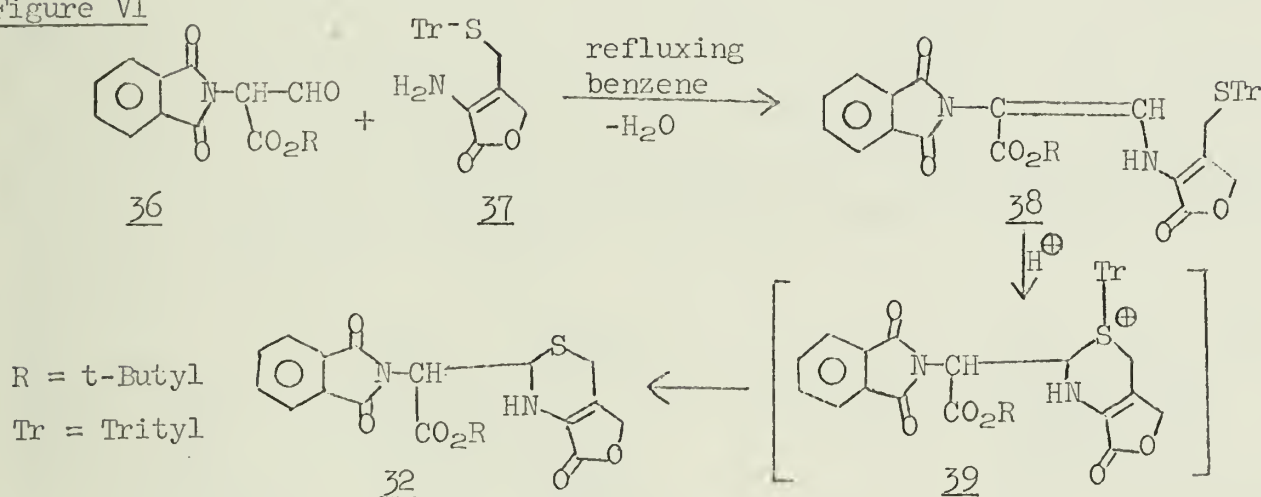
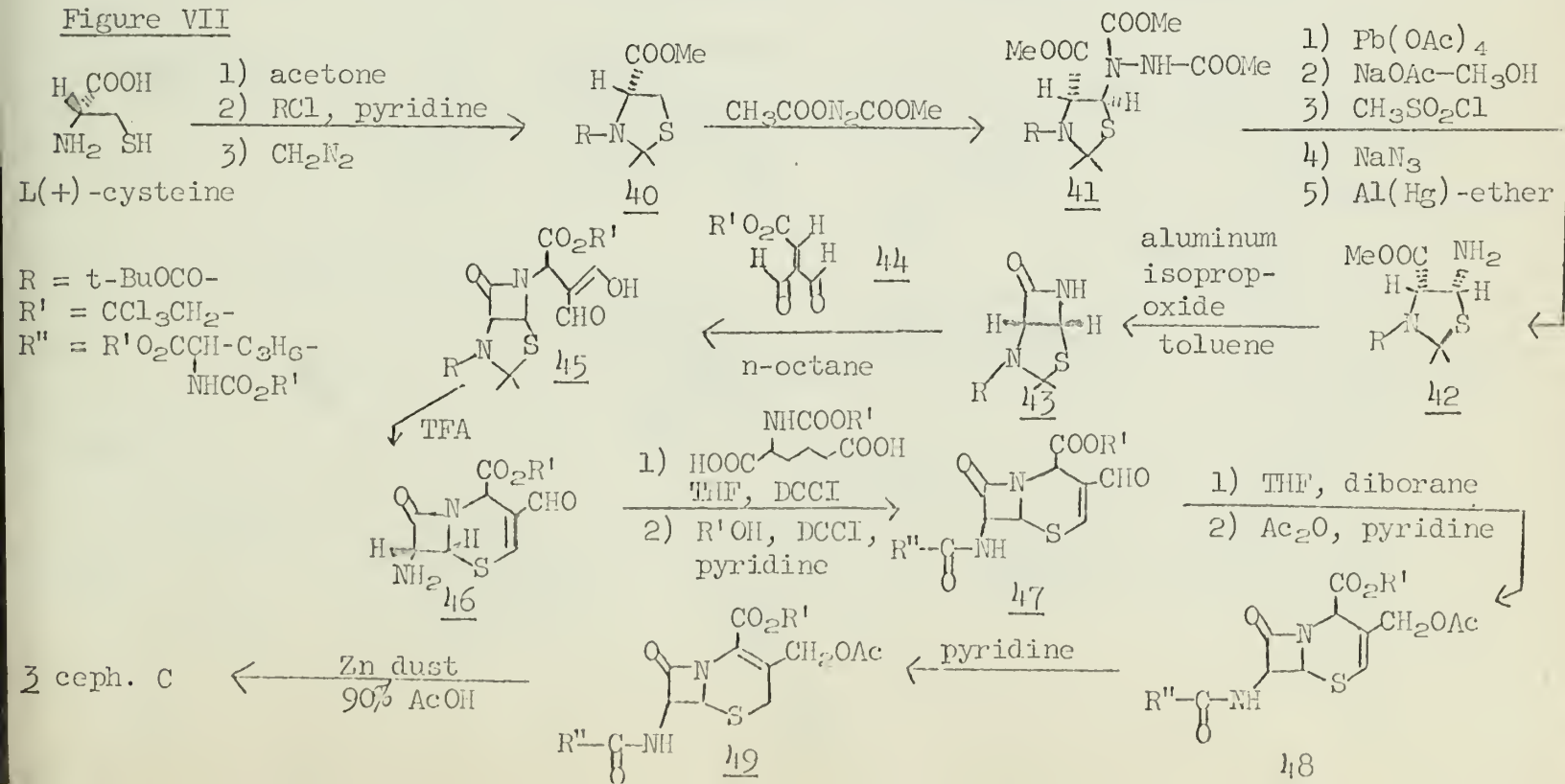


Figure VI



The first stereospecific synthesis of a cephalosporin was achieved by Woodward and co-workers.<sup>43</sup> Woodward deliberately avoided a route analogous to Sheehan's penicillin synthesis, pointing out the difficulty with stereochemical control and the extreme ease with which cephalosporin analogs of penicilloic acids decarboxylate.<sup>39,44</sup> In his Nobel Prize address,<sup>45</sup> Woodward explains with remarkable clarity the logic of his synthesis, which is summarized in Figure VII. The first transformation from cysteine

Figure VII





to 40 helps the stereospecificity of subsequent steps and improves the relative reactivity of the methylene. Even so, the functionalization of the methylene group was a difficult process, which was finally achieved stereospecifically using dimethyl azodicarboxylate to give 41. A series of substitutions eventually gave the azide with the correct stereochemistry, which was reduced to the amine 42. This was readily converted to 43, which in turn was condensed with 44, a unique dialdehyde containing a protected carboxyl group, to give 45. Treatment with trifluoroacetic acid effected ring closure and simultaneously removed all unwanted protecting groups. From this point, several conventional steps afforded cephalosporin C. Of special note is the use of the  $\beta,\beta,\beta$ -trichloroethyl protecting group. This group is removed by reduction and has proved to be generally useful.<sup>46</sup> The isomerization of the thiazine ring double bond will be discussed shortly.

A third method for cephalosporin synthesis uses the readily available penicillins as starting materials. Morin *et al.*<sup>47</sup> showed that  $\Delta^3$ -cephem compounds were obtained from the rearrangement of penicillin sulfoxides in acidic media. A later article<sup>48</sup> proposed the mechanism shown in Figure VIII, part of which is analogous to the *cis* elimination of sulfoxides studied by Kingsbury and Cram.<sup>49</sup> It remained to functionalize the 3-methyl group of desacetoxycephalosporins obtained by this route, a task accomplished by the transformations illustrated in Figure IX.<sup>50</sup> The oxidation going from 57 to 58 will be treated in a future paper by these authors. By means of a similar ring expansion scheme (Figure X), Stork and Cheung<sup>51</sup> have succeeded in synthesizing a properly substituted dihydrothiazine system, but it is unlikely that this work will be carried any further, as the work of the Squibb group<sup>39</sup> represents a more versatile approach to compounds of this type.

Figure VIII

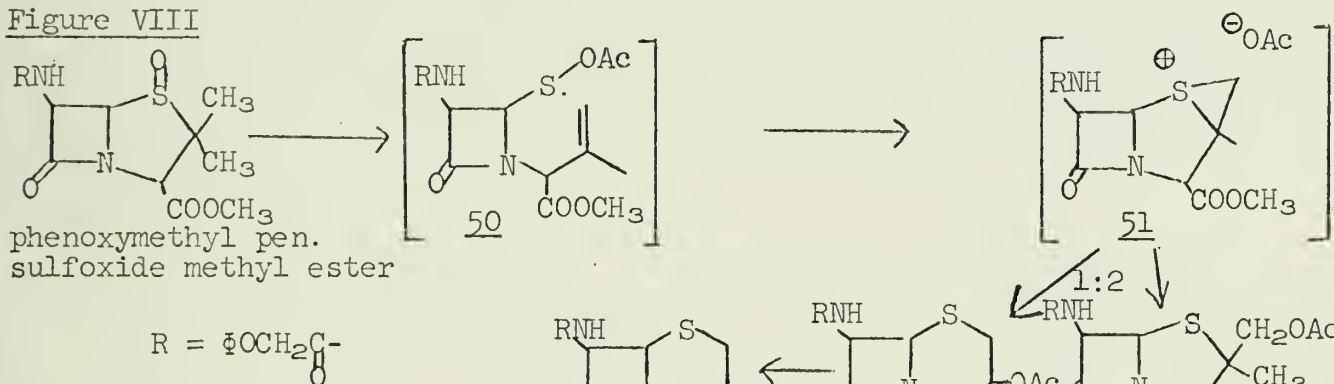


Figure IX

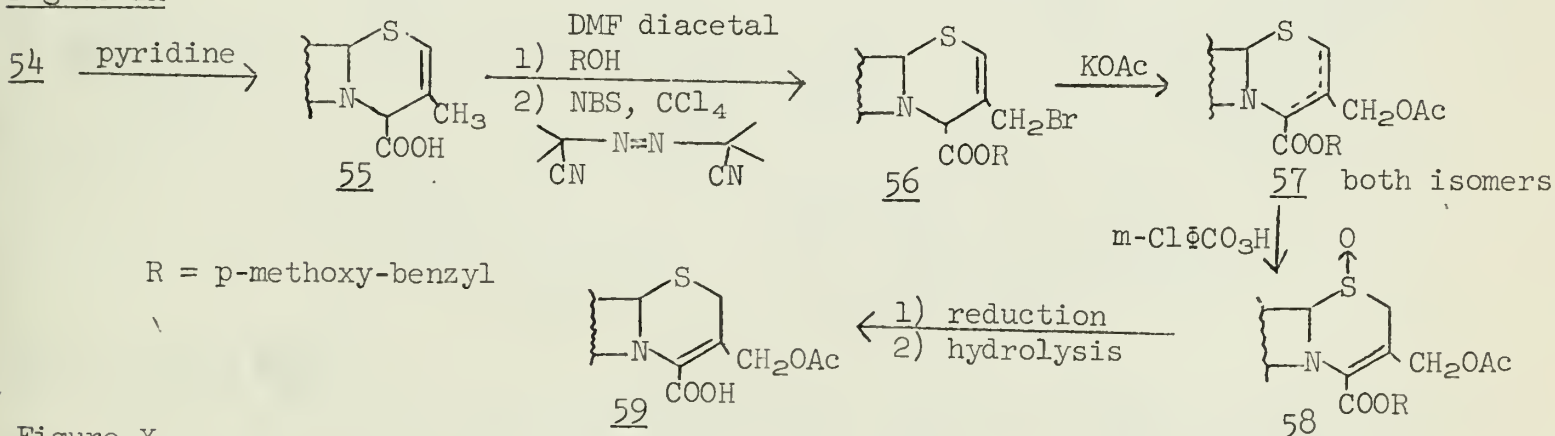
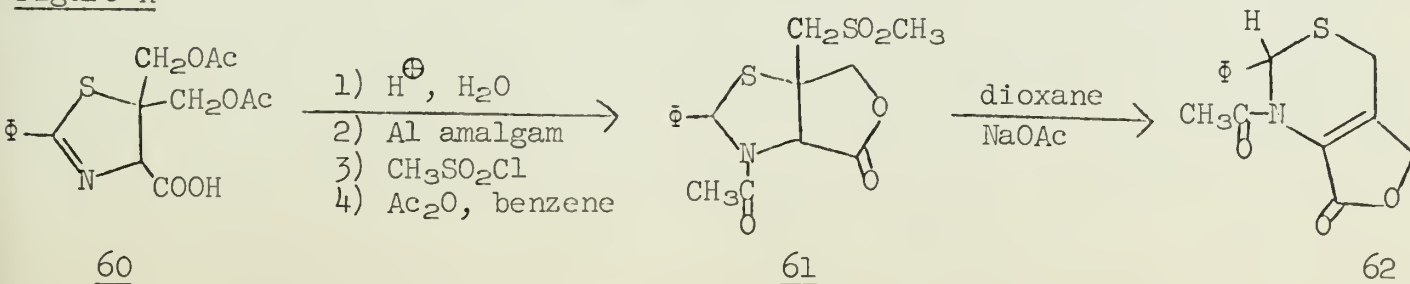


Figure X

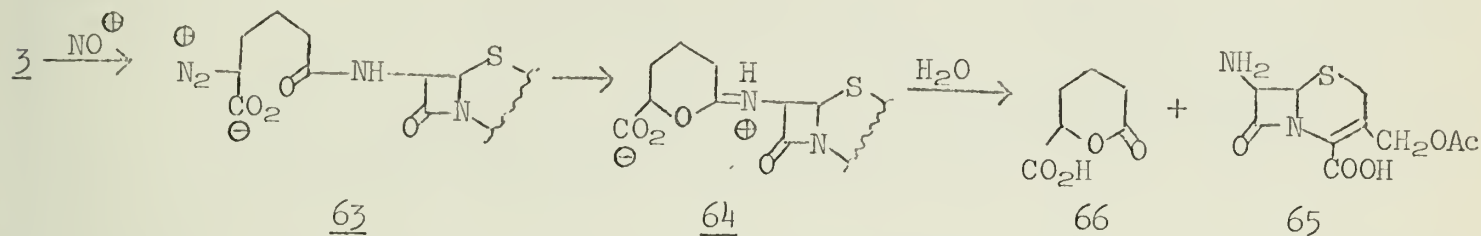




## SIDE CHAIN MODIFICATIONS

As with the penicillins, variations in the side chain of a cephalosporin have a profound effect on the molecule's antibiotic properties.<sup>13</sup> It was important, therefore, that ways be found to remove the natural substituents of cephalosporin C and replace them with other groups. 7-Aminocephalosporanic acid (7-ACA), 65, was obtainable in very low yield by controlled acid hydrolysis.<sup>52</sup> A more satisfactory method using nitrosyl chloride was developed,<sup>14</sup> which probably operates by the mechanism in Figure XI.<sup>53</sup> The free 7-amino group is easily acylated by a variety of reagents, and a large

Figure XI



number of derivatives have been synthesized and studied.<sup>52,54-58</sup> The 3-methylene group can readily be deacylated by the action of citrus acetyl esterase, an enzyme isolated from orange peel.<sup>59,60</sup> The resulting hydroxyl group reacts quickly with the 4-carboxyl under acidic conditions to form a lactone, which is given the trivial name cephalosporin C<sub>C</sub> (6, Figure II). Deacylation is not necessary, however, to change the 3-substituent. For reasons which will be discussed in the next section, the 3-methylene is susceptible to attack by a variety of sulfur and nitrogen nucleophiles.<sup>61-65</sup> A typical example, shown in Figure XII, is the reaction of cephalosporin C, 3, with pyridine to give cephalosporin C<sub>A</sub>, 67.<sup>61</sup> Several bidentate nucleophiles even form spiro compounds,<sup>64</sup> as shown in Figure XIII. Amides and esters of the 4-carboxyl group have been made using DCCI as the condensing agent, but yields were poor and the compounds showed little promise as antibiotics.<sup>66</sup> All of the above mentioned derivatives were tested for antibacterial activity, and structure-activity correlations have been made.<sup>13,54,67-69</sup> Two derivatives which have already achieved clinical success are cephalothin, 70,<sup>54,70</sup> and cephaloridine, 71.<sup>71,72</sup>

Figure XII

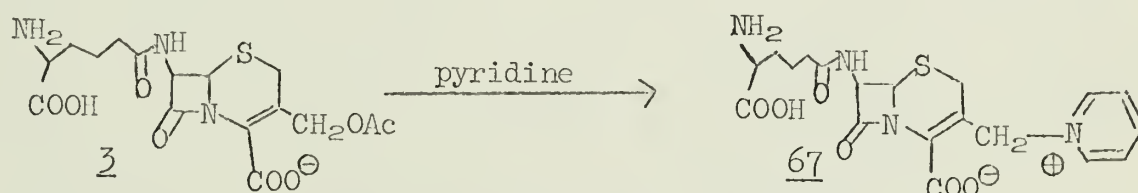
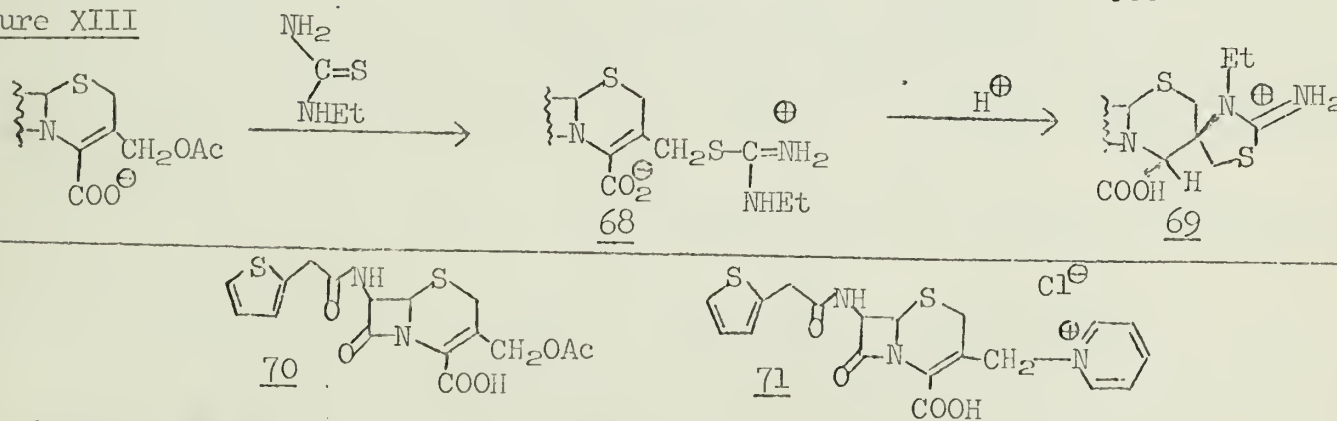


Figure XIII

THE  $\Delta^3$ -CEPHEM NUCLEUS

As can be seen from the degradation studies outlined in Figure II, the  $\Delta^3$ -cephem nucleus is rather labile under a variety of conditions. The  $\beta$ -lactam ring of  $\Delta^3$ -cephems is much more stable to acidic conditions than that of the corresponding penicillins, but is still very susceptible to basic cleavage.<sup>11</sup> Even more stable is the  $\beta$ -lactam ring of the  $\Delta^2$ -cephems.<sup>73</sup> There appears to be a correlation between ring strain and the instability of the  $\beta$ -lactam. Morin *et al.*<sup>48</sup> have shown that there is a direct correlation between the acylating ability of the  $\beta$ -lactam of a cephalosporin as measured by its infrared carbonyl stretching frequency and the biological activity of that compound. It is interesting to note that the  $\beta$ -lactam of a  $\Delta^3$ -cepham compound does not cleave in a simple manner but is accompanied by extensive rearrangement, as is evidenced by the evolution of acetic acid and the loss of the 260 nm absorption band.<sup>36,74</sup>



The dihydrothiazine ring of the  $\Delta^3$ -cepham system is an unusual grouping, containing at once an enamine, an allylic sulfide, an allylic acetoxy group, and an  $\alpha,\beta$ -unsaturated acid. In weakly basic solution, the double bond isomerizes, and an equilibrium between the  $\Delta^3$  and  $\Delta^2$  compounds is established which favors the  $\Delta^2$  isomer by a ratio of about 7 to 3.<sup>73</sup> The rate of equilibration for esters is much faster than for free acids, presumably because of the increased acidity at the 2-position.<sup>73</sup> Nucleophilic substitutions at the 3-methylene group occur readily with both  $\Delta^3$  and  $\Delta^2$  compounds when the substituent at the 4-position is a free carboxylate ion, but no reaction is observed when the 4-carboxyl group is esterified.<sup>65,75</sup> A kinetic study<sup>75</sup> of the reaction with pyridine in aqueous solution showed the reaction to be first order in substrate and zero order in pyridine. An S<sub>N</sub>1 mechanism was proposed, with the rate constant for the  $\Delta^3$  compounds being  $2 \times 10^{-5} \text{ sec}^{-1}$ . A rate one fifth as large was observed with the  $\Delta^2$  isomers. The lack of reactivity shown by the esters has been interpreted<sup>73,75</sup> as an indication that the carboxylate ion is an important factor in the stabilization of the positive charge developed during this type of reaction.

## CONCLUSIONS

Cephalosporin C antibiotics display an interesting chemistry which, although closely related to penicillin chemistry, is unique in many ways. Several excellent reviews are available on aspects of this subject which were not covered in this seminar. The biosynthesis,<sup>76</sup> mode of action,<sup>13</sup> behavior with enzymes,<sup>74</sup> structure-activity relationships<sup>1,13</sup> and manufacture<sup>13</sup> of cephalosporins all have an extensive literature. In addition, the patent literature contains literally hundreds of syntheses for drugs of this type.

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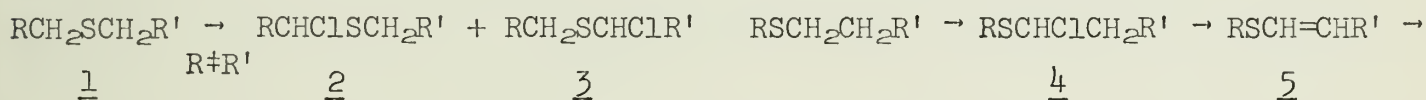
# α-CHLORINATION OF SULFIDES

Reported by Makoto Yamaye

October 16, 1969

α-Chloro sulfides have much utility as synthetic intermediates of organic chemistry.<sup>1</sup> One of the most common synthetic methods for forming α-chloro sulfides involves the chlorination of sulfides with an appropriate chlorinating agent. Chlorination of dimethyl sulfide with chlorine was first reported by Riche.<sup>2</sup> Since the reaction is exothermic and somewhat difficult to control, it often leads to the formation of a mixture of polychlorination and decomposition products. Other common chlorinating agents so far used are sulfonyl chloride<sup>3,4</sup> and N-chlorosuccinimide (NCS).<sup>5</sup> Use of these reagents in inert solvents makes it possible to carry out more regulated chlorinations of a variety of sulfides and facilitates the isolation and characterization of the chlorinated products.

The chlorination takes place at the carbon atom α to the sulfur atom of sulfides. Thus at least one α hydrogen atom is required for this reaction. With appropriate reaction conditions, a symmetrical sulfide produces only a single α-chloro sulfide while unsymmetrical sulfides 1 usually afford two isomeric α-chloro sulfides 2 and 3. Most α-chloro sulfides thus formed 4 are relatively unstable when they carry β hydrogens. Use of sulfonyl chloride or chlorine as a chlorinating reagent often induces elimination of hydrogen chloride to afford the α,β-unsaturated sulfides 5 which undergo further undesirable reactions. This is not the case in the NCS chlorination. Therefore NCS may have an advantage over the other chlorinating agents.

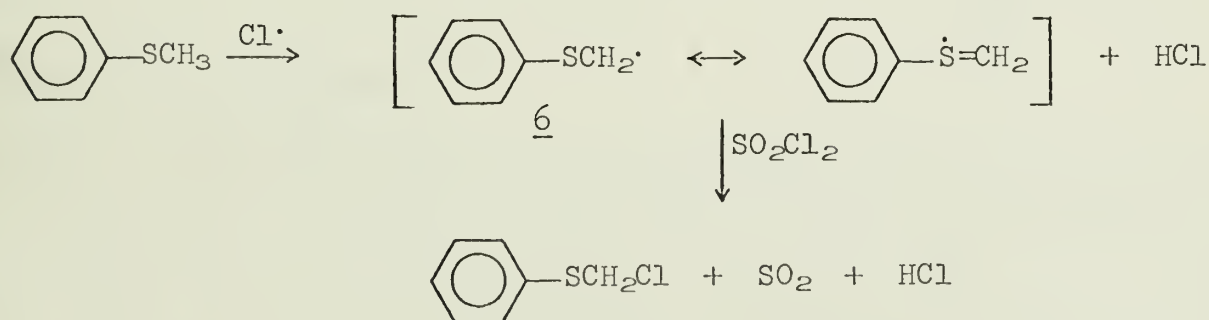


The mechanistic features of this reaction have not been completely unveiled. However, it is likely that the reaction has a resemblance to the Pummerer reaction, the traditional name for the reaction of sulfoxides with acid anhydrides to produce the corresponding α-acetoxy sulfides.<sup>6</sup>

This seminar will follow the development of the mechanistic investigations of the α-chlorination reaction.

## FREE RADICAL INTERMEDIATES

Price and Oae<sup>7</sup> suggest a free radical mechanism for chlorination reactions with sulfonyl chloride. Taking methyl phenyl sulfide as an example, they assume a radical intermediate 6 which might be stabilized by resonance due to the 3d shell expansion of the sulfur atom.



There have been, however, two kinds of experimental observations against this mechanism. One is the observations of a transitory intermediate, presumably a chlorosulfonium salt, in several chlorinations at relatively low temperatures.<sup>4,8,9</sup> Böhme *et al.*<sup>8</sup> reported the reaction of dimethyl sulfide with chlorine in carbon tetrachloride at -20°. The resulting crystalline "so-called sulfide dichloride" was filtered and warmed to room temperature. Release of hydrogen chloride afforded monochloro dimethyl sulfide. The other contradictory fact is the directive effects in chlorinations of unsymmetrical sulfides which carry electron-withdrawing groups such as cyano or carbomethoxy group or substituted phenyl rings at the α position.

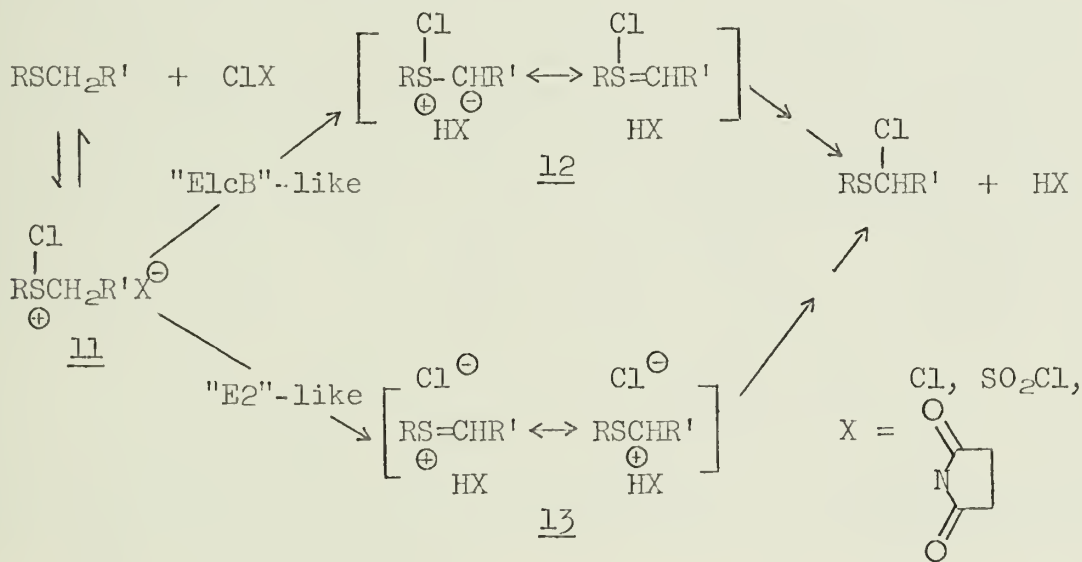


Ethylmercaptoacetonitrile 7 reacts with NCS in carbon tetrachloride to produce 2-chloro-2-ethylmercaptoacetonitrile 8.<sup>10</sup> Treatment of methyl 2-methylmercaptoacetate 9 with two equivalents of chlorine in carbon tetrachloride yields methyl 2,2-dichloro-2-methylmercaptoacetate 10.<sup>11</sup> If a free radical mechanism were to operate in these cases, a chlorine radical might be expected to attack the opposite methylene or methyl group, due to its electrophilic character. Substituent effects in the chlorination of dibenzyl sulfides, which will be discussed later, are more clearly incompatible with this radical mechanism.



#### CHLOROSULFONIUM SALT INTERMEDIATES

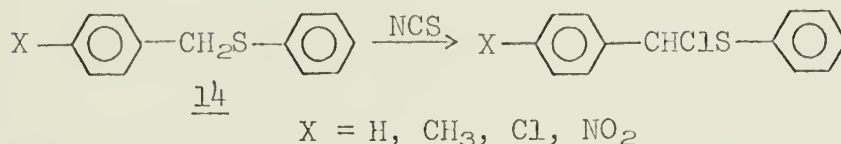
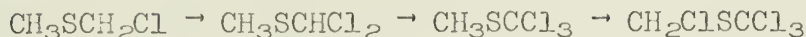
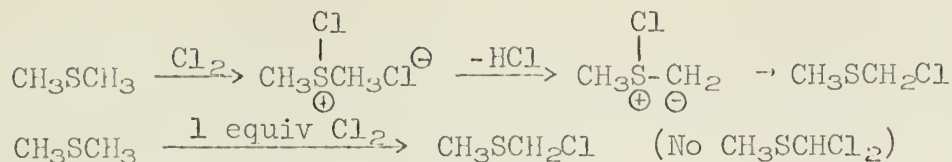
A general mechanistic scheme for the  $\alpha$ -chlorination of sulfides postulates a chlorosulfonium salt 11 as a common intermediate. Two mechanistic extremes, which have support in one or another system, can be discussed in terms of their analogs in olefin forming eliminations. The "E1cB"-like path assumes an abstraction of an acidic  $\alpha$  proton through a transition state resembling ylid 12, with subsequent migration of chlorine from the sulfur to the  $\alpha$  carbon. The "E2"-like path involves a concerted elimination of HX from the chlorosulfonium salt 11 to approach carbonium ion 13 at the transition state. The carbonium ion thus formed would be attacked by the chloride anion to afford the product.



#### Intermolecular Competitions

Historically, Böhme *et al.*<sup>8</sup> first proposed the ylid mechanism based upon the observation of the chlorine chlorination of dimethyl sulfide in carbon tetrachloride at  $-20^\circ$ . Chlorination of dimethyl sulfide with an excess of a chlorinating agent produced mono-, di-, tri- and tetrachloro sulfides successively.<sup>3</sup> This means that the rate of chlorination of dimethyl sulfide is much faster than that of chloromethyl methyl sulfide and so forth. The decrease in rate with increased chlorination suggests an increase in positive charge on going to the rate determining transition state. This was confirmed by the competitive chlorination of benzylic sulfides 14 in carbon tetrachloride with NCS.<sup>12</sup> The relative rates of benzylic chlorinations were correlated by the Hammett  $\sigma_p$  treatment to afford a  $\rho$  value of  $-0.8$ . The negative  $\rho$  value indicates an increase in positive charge in the rate-determining transition states, a finding compatible with a rate-determining reaction forming or destroying the postulated chlorosulfonium salt 11.

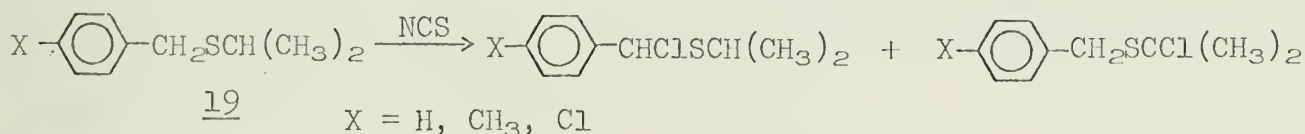
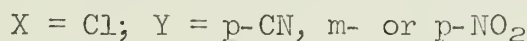
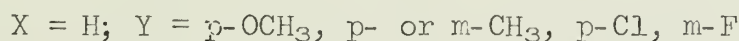
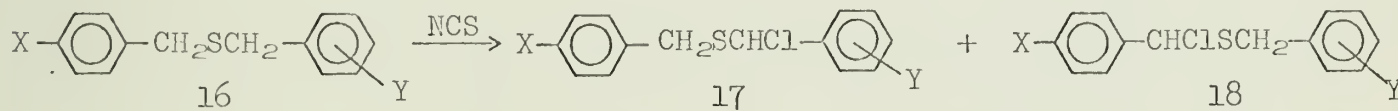




### Intramolecular Competitions

The isotope effect in the NCS chlorination of  $\alpha$ -d-benzyl phenyl sulfide 15 was determined.<sup>12</sup> Using quantitative nmr, a comparison of the area of methylene signal of 15 to that of the methinyl peak of  $\alpha$ -chloro-benzyl phenyl sulfide in the products gave an average value of  $k_H/k_D$  of 5.7. This primary isotope effect implies that the rate-determining step cannot appear after ylid formation, i.e., that the loss of a proton from the chlorosulfonium salt 11 is not reversible.

The intramolecularly competitive chlorinations of unsymmetrical benzylic sulfides 16 with NCS in carbon tetrachloride were carried out.<sup>13</sup> The resulting mixtures of  $\alpha$ -chloro sulfides 17 and 18 were analyzed by integration of the methinyl hydrogen singlets in the nmr spectra of the crude reaction products. Correlation of these data by a Hammett treatment gives a  $\rho$  value of  $1.05 \pm 0.04$ . A nearly equal positive  $\rho$  value (1.1) was obtained in the NCS chlorinations at the benzylic positions of benzyl isopropyl sulfides 19 in an intramolecular competition between benzyl and isopropyl chlorination.<sup>10</sup> These positive  $\rho$  values are incompatible with a radical mechanism since



a negative  $\rho$  value ( $-0.76 \pm 0.03$ ) is obtained for the competitive chlorinations of substituted toluenes using chlorine and light.<sup>14</sup>

The positive  $\rho$  values obtained indicate that preferential abstraction of the more acidic proton takes place through a transition resembling ylid 12 ("E1cB"-like) rather than carbonium ion 13 ("E2"-like). A comment may be useful about  $\rho$  values obtained in inter- and intramolecular competitions. Intermolecular competitions give data which can be used to probe charge distribution in the rate determining step compared with that in the starting material. On the other hand, intramolecular competitions give values which reflect differences in charge distribution for two competing product-determining reactions from the same intermediate (11 in this scheme).

Among  $\alpha$ -chlorinations of sulfides it seems very likely that 2-ethylmercaptoacetone nitrile 7, methyl 2-methylmercaptoacetate 9 and dicarboalkoxymethyl sulfides 20 (R = CH<sub>3</sub>,<sup>8</sup> CH<sub>3</sub>CH<sub>2</sub>,<sup>4</sup>) proceed via the "E1cB"-like mechanism. These sulfides all carry relatively more acidic protons at the  $\alpha$  carbon, which may be easily abstracted with the base to form a ylid 12.





During chlorination of dimethyl sulfide with an excess of a chlorinating agent, complete chlorination of one methyl group occurs before the other methyl group is attacked.<sup>3</sup> This observation is in accord with the increasing acidity of the  $\alpha$  protons by the strong inductive effect of the chlorines attached to the  $\alpha$  carbon. Other  $\alpha$ -chloro sulfides 21, 22,<sup>10</sup> 23, 24<sup>15</sup> and 25<sup>16</sup> behave in the same way, giving further chlorination at the carbon already chlorinated.

Tuleen *et al.*<sup>10</sup> studied the chlorinations of sulfides 21, 22 and 7 by NCS in carbon tetrachloride at 4°. The resulting mixtures of  $\alpha$ -chloro sulfides were analyzed by integration of appropriate signals in the nmr spectra of the crude reaction products. The ratio of the major to the minor component in the resulting chloro sulfide mixture is shown in Table 1. In each case the carbon to which the electronegative substituent is attached is the site of preferential chlorination. Chlorination of ethylmercaptoacetonitrile 7 gave 2-chloro-2-ethylmercaptoacetonitrile as the sole product. From this table one can see that the directive effect seems to be proportional to the magnitude of the electron-withdrawing effect of the  $\alpha$  substituents. The carbomethoxy substituent (see sulfide 9) demonstrates a similar directive influence.<sup>11</sup>

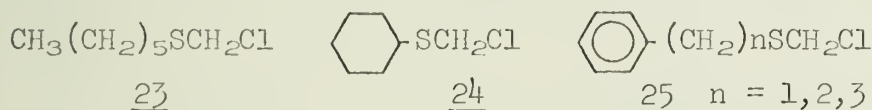
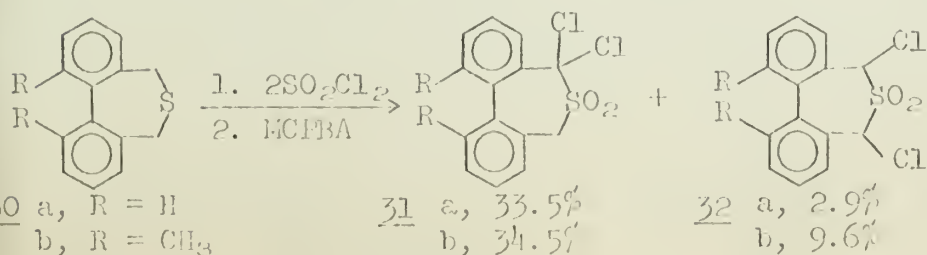
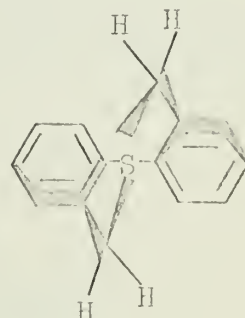
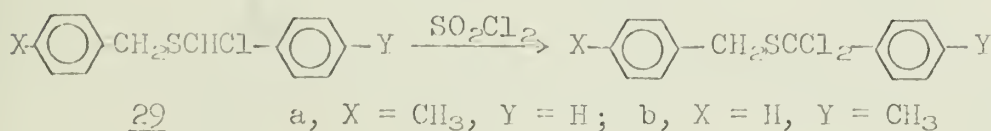
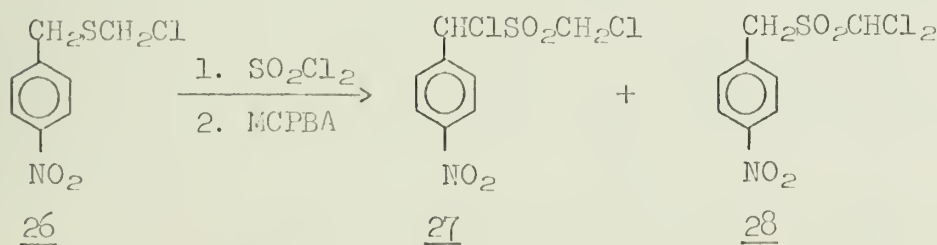


Table 1

<u>21</u> , $\text{CH}_3\text{CH}_2\text{SCH}_2\text{Cl}$	<u>25</u> $\pm$ 3
<u>22</u> , $(\text{CH}_3)_2\text{CHSCH}_2\text{Cl}$	$7.9 \pm 0.3$
<u>7</u> , $\text{CH}_3\text{CH}_2\text{SCH}_2\text{CN}$	$\infty$

Phenyl and substituted phenyl groups cannot compete in directive influence with a chlorine substituent.<sup>16,17</sup> There is, however, one exception to this generalization which has so far been observed. The *p*-nitrophenyl group shows a stronger directive influence than does chlorine atom, although the difference is small. Chlorination of chloromethyl *p*-nitrobenzyl sulfide 26 with one equivalent of sulfonyl chloride followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) gives the isomeric dichloro sulfones 27 and 28 in a ratio of 3:2.<sup>17</sup> Although chloro sulfides 29 show the predicted directive effect,<sup>15</sup> 2,7-dihydro-3,4,5,6-dibenzothiepins 30 yield two isomeric dichloro sulfones 31 and 32 upon treatment with two equivalents of sulfonyl chloride followed by the MCPBA oxidation.<sup>18</sup> The proposed intermediate sulfonium salt has two alternatives open to it. One affords the  $\alpha, \alpha$ -dichloro sulfide 31 in a reaction which reflects the strong inductive effect of the first  $\alpha$ -chloro substituent. The other, leading to the  $\alpha, \alpha'$ -dichloro isomer 32, can be supposed to be favored by the geometry of the system. From an inspection of Dreiding models it seems reasonable to suppose that one of the two methylene hydrogens on one carbon should be more easily replaced than the other. This steric effect would therefore favor the formation of  $\alpha, \alpha'$ -dichloro isomer with this hydrogen replaced by chlorine on each of the methylene carbons. The product ratio indicates that there still exists a strong directive influence of chlorine atom.





The positive  $\rho$  values obtained for intramolecular competitions in the dibenzyl sulfides parallel directive effects in all  $\alpha$ -chlorination reactions of sulfides which have been reported except those of unsymmetrical aliphatic sulfides.

Ethyl methyl sulfide 33, the simplest unsymmetrical aliphatic sulfide, was treated with chlorine to produce  $\alpha$ -chloroethyl methyl sulfide 34.<sup>19</sup> Attempted  $\alpha$ -chlorination of isopropyl methyl sulfide 35, with chlorine produced 2-chloro-1-methylvinyl methyl sulfide 36, probably via  $\alpha$ -chloro sulfide 37.<sup>19</sup> Using NCS as a chlorinating agent, Tuleen *et al.*<sup>5,10</sup> investigated the more controlled chlorination of unsymmetrical aliphatic sulfides. The ratio of the major to the minor component in the crude product is shown in Table 2. Preferential attack of chlorine occurs at the site of the more highly substituted carbon. These observations may be interpreted in terms of the "E2"-like mechanism in which the  $\alpha$  carbon develops carbonium ion character in the transition state.

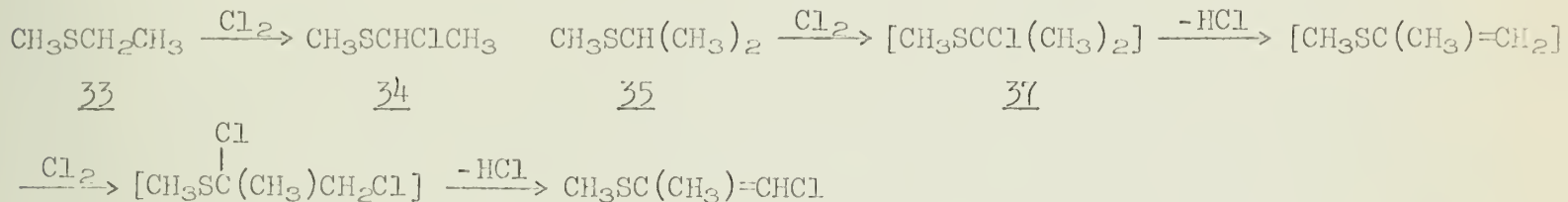


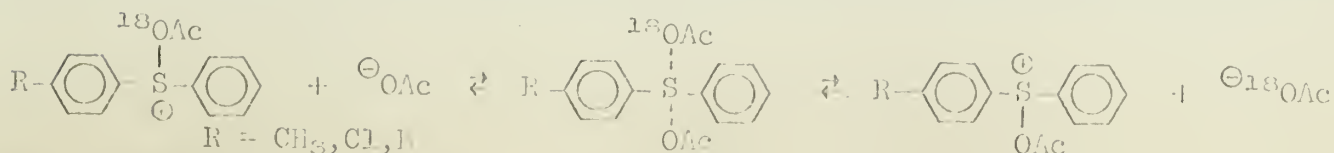
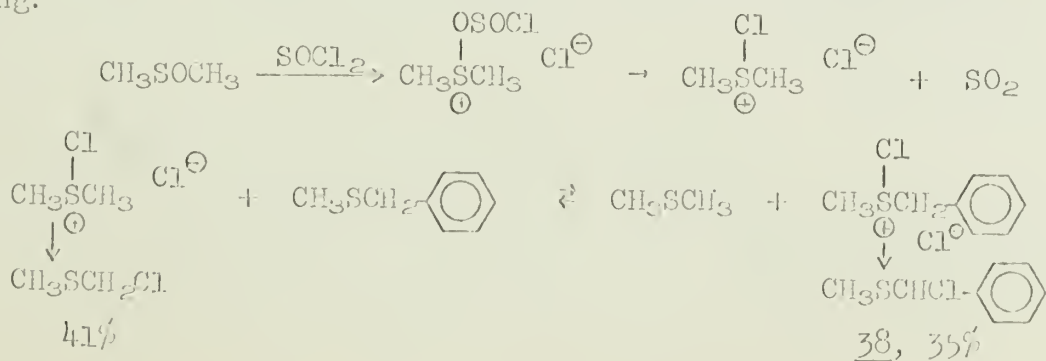
Table 2

$\text{CH}_3\text{SCH}_2\text{CH}_3$	$3.4 \pm 0.2$
$\text{CH}_3\text{SCH}_2\text{CH}_2\text{CH}_3$	$3.7 \pm 0.1$
$\text{CH}_3\text{SCH}(\text{CH}_3)_2$	$\sim 10$
$\text{CH}_3\text{CH}_2\text{SCH}(\text{CH}_3)_2$	$2.4 \pm 0.4$

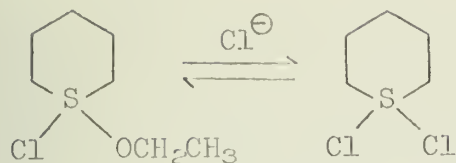
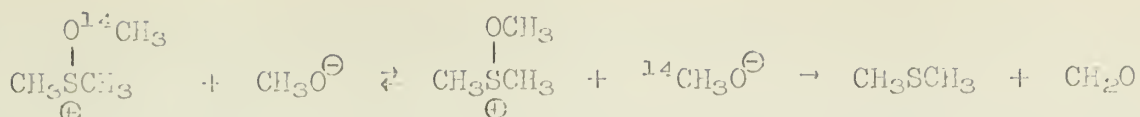
#### Reversibility of Chlorosulfonium Salt Formation

Bordwell *et al.*<sup>4</sup> investigated the reaction of dimethyl sulfoxide and benzyl methyl sulfide with one equivalent of thionyl chloride in methylene chloride. They rationalized the formation of  $\alpha$ -chlorobenzyl methyl sulfide 38 with the postulate of a reversible process of chlorosulfonium salt formation. Benzyl methyl sulfide when treated alone with thionyl chloride in the similar manner did not form the  $\alpha$ -chloro sulfide.

The "E1cB"-like mechanism suggested here is closely analogous to that for the Pummerer reaction.<sup>20</sup> Acetoxy exchange in the Pummerer reaction has been observed.<sup>21</sup> The reaction was carried out by heating optically active <sup>18</sup>O-labelled sulfoxides in excess acetic anhydride at 120°. The exchange reaction is suggested to involve S<sub>N</sub>2' type inversion in the rate-determining step since the rate of racemization of phenyl p-tolyl sulfoxides was twice that of the oxygen exchange. This was also confirmed by the observation of a small effect of substituents on the rate of the reaction and a large negative value (-28.6 eu) for the entropy of activation. A scrambling study of the reaction of dimethylmethoxysulfonium-O-<sup>14</sup>C salt with methoxide anion indicates that the methoxy exchange occurs much more rapidly than elimination to methyl sulfide and formaldehyde.<sup>22,23</sup> Recently Johnson *et al.*<sup>24</sup> suggested a rapid exchange of chlorine and ethoxy group on a proposed tetravalent sulfur atom in the thiane system based on the observation that using radioactive ethanol, ethoxy exchange in the ethoxysulfonium salt was found to be very fast at room temperature only in the presence of a catalytic amount of a chloride ion. With these analogies in mind one might expect the exchange of chlorine in 11 to be fast. This would make the second step of the reaction sequence, the loss of a proton, rate-determining.

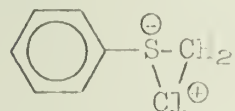






### Chlorine Transfer from Sulfur to Carbon

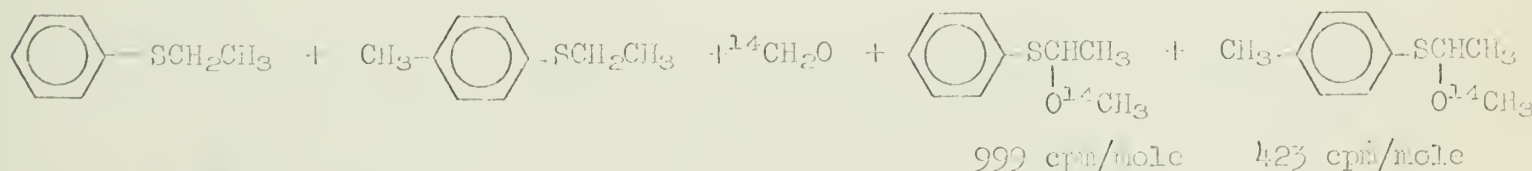
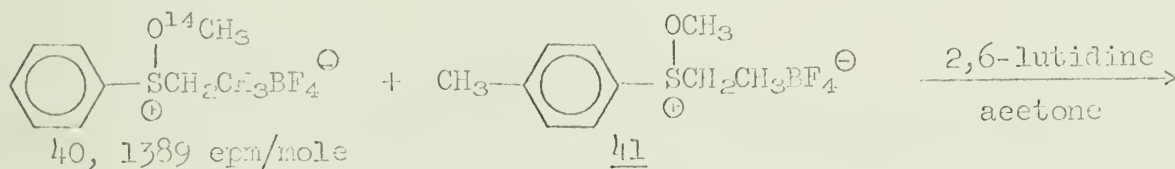
A choice between intra- and inter-molecular paths for chlorine transfer from sulfur to the  $\alpha$  carbon is not obvious in Böhme's mechanism. Truce *et al.*<sup>3</sup> suggest intramolecular transfer. Upon treatment of  $\alpha, \alpha$ -dichloro dimethyl sulfide with sulfuryl chloride in the presence of a high concentration of bromine,  $\alpha, \alpha, \alpha$ -trichloro dimethyl sulfide was the sole product isolated. They concluded that chlorine transfer may be taking place as the proton is being removed. Neither the yield of the product nor experimental details were reported. A possibility such as the halogen exchange reaction of bromomethyl methyl sulfide with chloride ion has not been checked. Bordwell *et al.*<sup>4</sup> also proposed internal 1,2-shift of the chlorine atom. They postulate a three-membered ring intermediate 39. In the closely analogous rearrangement of alkoxysulfonium salt, oxygen-18 tracer studies have suggested that this step is either intermolecular or that it involves an ion pair intermediate such as:



39



Johnson *et al.*<sup>20, 25</sup> carried out a crossover experiment using phenylethylmethoxy-sulfonium-O-<sup>14</sup>C salt 40 and *p*-tolylethylmethoxysulfonium salt 41 in 2,6-lutidine-acetone, a base-solvent system which does not exchange with the alkoxysulfonium salts. Appropriate control experiments eliminated the possibility of a scrambling of the label after the products formed. The results were interpreted in terms of methoxy group ionization from the sulfur ylid. Use of more polar solvents is more favorable for the stabilization of the carbonium ion-methoxide anion pair which is formed, resulting in preferential formation of  $\alpha$  rearrangement products (increasing from 0% to 80%  $\alpha$ -substitution on going from tetrahydrofuran to methanol).



### The Continuum of "E1cB"-like and "E2"-like Mechanisms

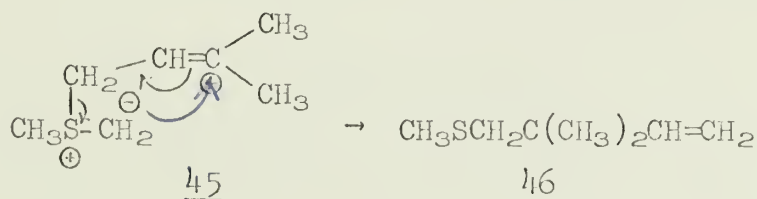
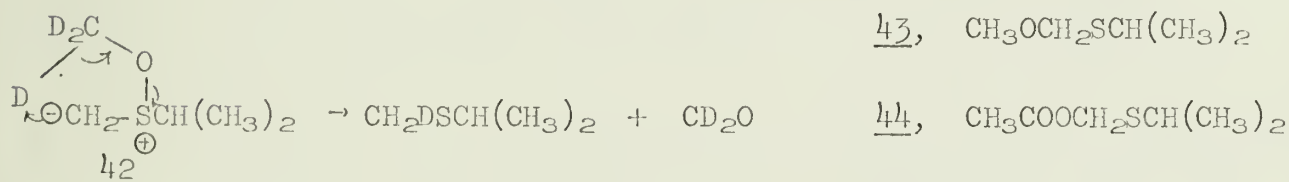
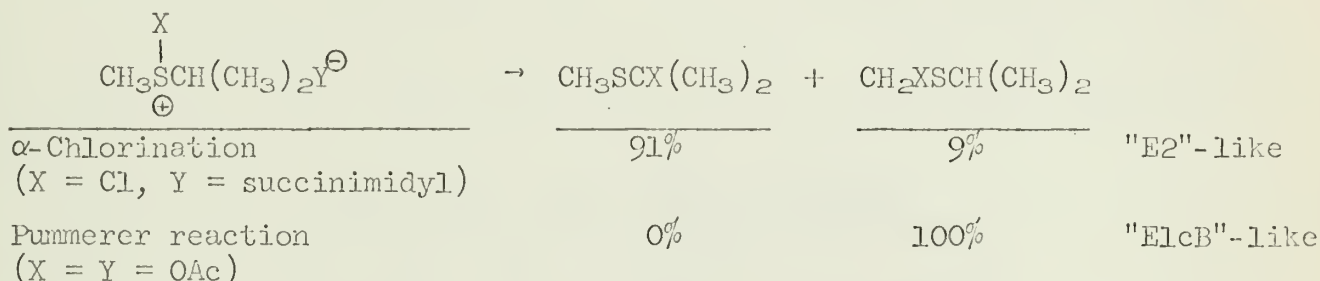
In the two mechanisms discussed above the difference lies in the degree of stabilization of the positive charge left behind upon loss of chloride ion. They are considered to be two extremes in the "E1cB"-like-"E2"-like spectrum in analogy with the E1-E2-E1cB spectrum of mechanism for olefin formation. The E1 analog seems less likely here since it would involve the introduction of two positive charges on sulfur.



There has been, however, no evidence for distinguishing whether postulated 12 and 13 are intermediates or merely transition states.

### Effect of Leaving Groups

Chloride anion seems to be the best leaving group compared with others in a variety of reactions whose proposed mechanisms are closely related to the  $\alpha$ -chlorination of sulfides. An example is available for quantitative comparison of product ratios in the  $\alpha$ -chlorination<sup>10</sup> and the Pummerer reaction<sup>20</sup> of the comparable starting material. With the less effective acetate leaving group, the spectrum seems to shift far towards the "ElcB"-like extreme. If isopropylmethylmethoxysulfonium fluoroborate ( $X = OCH_3$ ,  $Y = BF_4$ ) is treated with sodium methoxide in methanol, only isopropyl methyl sulfide is formed via cyclic transition state involving ylid 42.<sup>20,22</sup> No  $\alpha$ -rearrangement products are formed. However, if the same salt is added to a solution of sodium acetate in dimethyl sulfoxide, the  $\alpha$ -rearrangement product 43 (20%) is obtained with the  $\alpha$ -acetoxy product 44 (69%) as a major component. This suggests the intervention of the acetoxysulfonium salt, indicating the poorer leaving ability of methoxy group. The allyl group, probably a far less effective leaving group, behaves in a similar manner.  $\gamma,\gamma$ -Dimethylallyldimethylsulfonium salt (see 45) was treated with *n*-butyllithium to form the homoallyl sulfide 46.<sup>28</sup> This reaction is synthetically useful and of possible importance in biosynthesis.



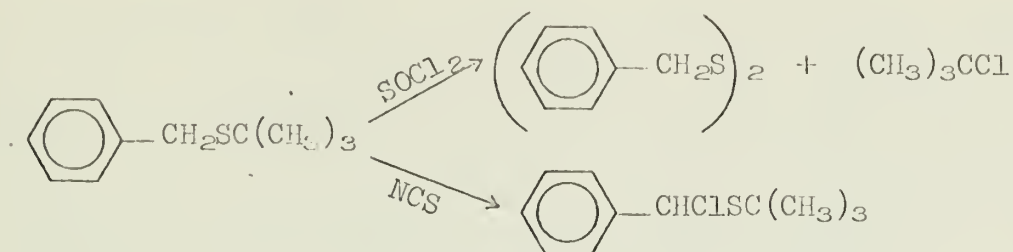
### Effect of Bases

The sulfuryl chloride chlorination of benzyl *t*-butyl sulfide resulted in fragmentation to form *t*-butyl chloride and dibenzyl disulfide.<sup>10</sup> This fragmentation was considered to be facilitated by formation of the stable *t*-butyl cation. The same sulfide was treated with NCS to yield the normal chlorination product.<sup>10</sup> This observed difference was interpreted in terms of nature of chlorinating reagents. When NCS is employed, the succinimidyl anion is basic enough to abstract the  $\alpha$  hydrogen rapidly before fragmentation occurs. In case of sulfuryl chloride, the chloride anion, a weaker base, removes the  $\alpha$  hydrogen too slowly to compete with fragmentation.

It seems likely that the formation of the  $\alpha,\beta$ -unsaturated sulfides is caused by hydrogen chloride produced during the sulfuryl chloride or chlorine chlorination. This may be explained with the ionization of the  $\alpha$  chlorine as an anion catalyzed by hydrogen



chloride followed by removal of the  $\beta$  proton with the chloride ion.<sup>4</sup> The NCS chlorination, however, does not produce hydrogen chloride and gives a satisfactory result in most cases. The four-membered cyclic sulfides undergo ring cleavage during chlorination due to steric strain.<sup>27</sup>



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# SOME RECENT EXAMPLES OF THE SYNTHESIS OF BRIDGED TRICYCLIC SESQUITERPENE AND SESQUITERPENOID SYSTEMS

Reported by Roger L. Sowerby

October 20, 1969

## INTRODUCTION

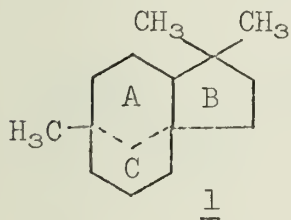
Sesquiterpenes offer a wide and varied spectrum of structural types to challenge the synthetic chemist. The structures vary from acyclic compounds to complex polycyclic compounds with many asymmetric centers.<sup>1</sup> This seminar will discuss some recent approaches to the synthesis of tricyclic sesquiterpenes which contain at least one bridging carbon atom. The emphasis will be on the key intermediates and key reactions which are used in the synthetic sequence. Besides the examples given here, other examples of recent syntheses of this type of compound are copaenc,<sup>2,3</sup>  $\alpha$ -santalol,<sup>4</sup> isolongifolene,<sup>5</sup> cedrol,<sup>6</sup> and patchouli alcohol.<sup>7</sup>

In most syntheses there are one or two key steps around which the entire sequence of steps is built.<sup>8</sup> These steps usually involve a reaction which establishes the stereochemistry about an asymmetric center, formation of a bridge at the proper sites, or expansion of a ring at the proper position. Therefore the reaction sequence must be carefully planned so that the key compound and key reactions will give the desired results.

## THE TRADITIONAL APPROACH

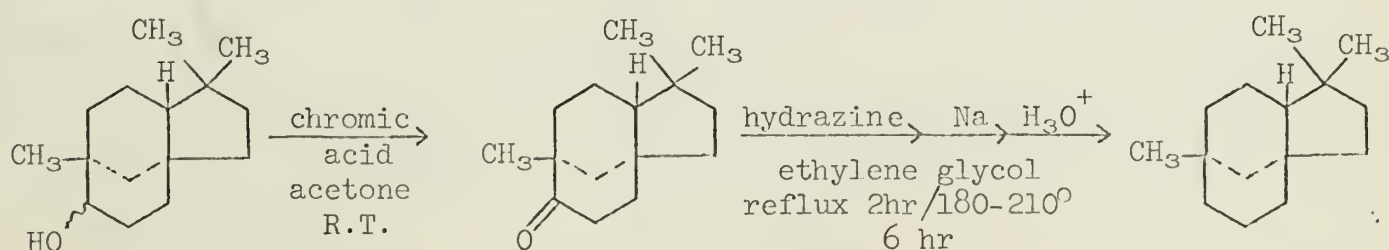
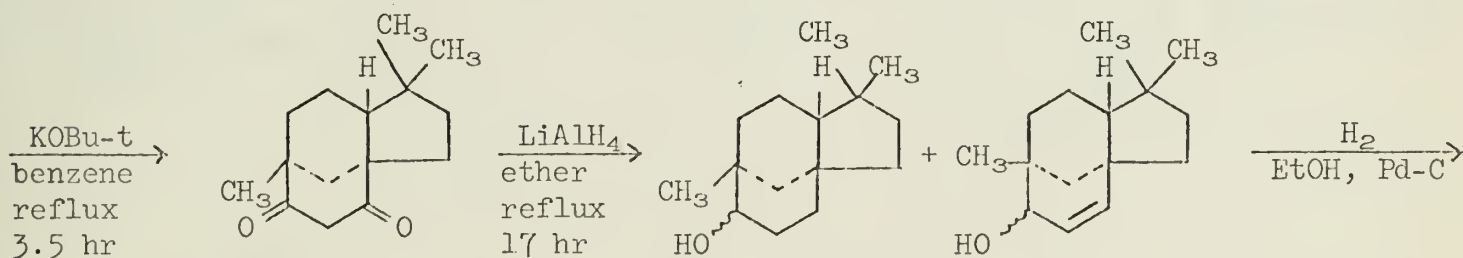
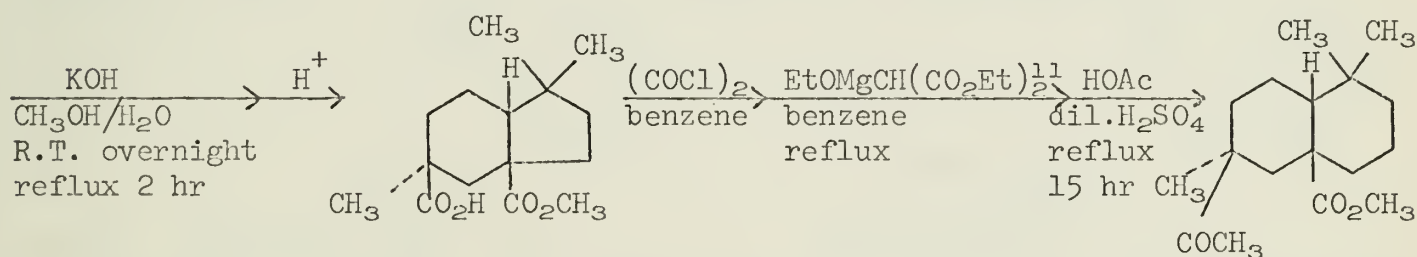
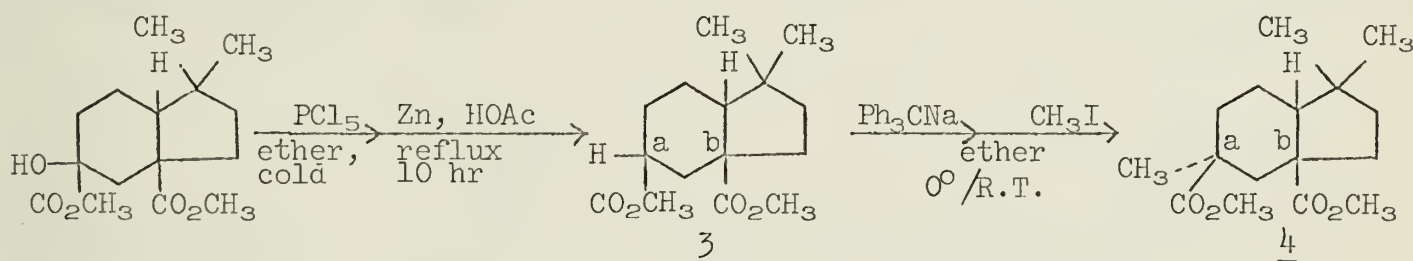
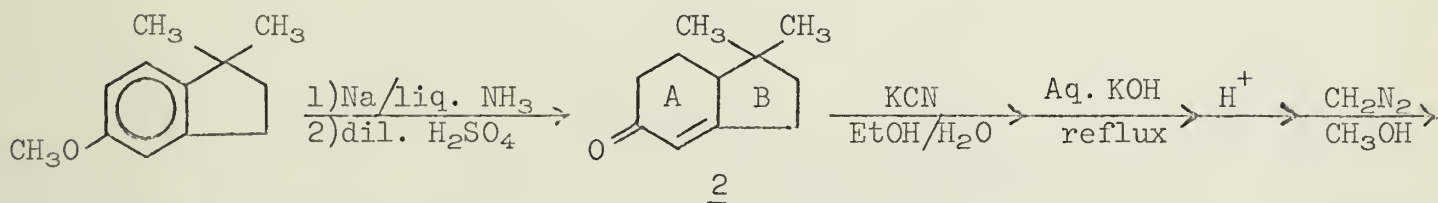
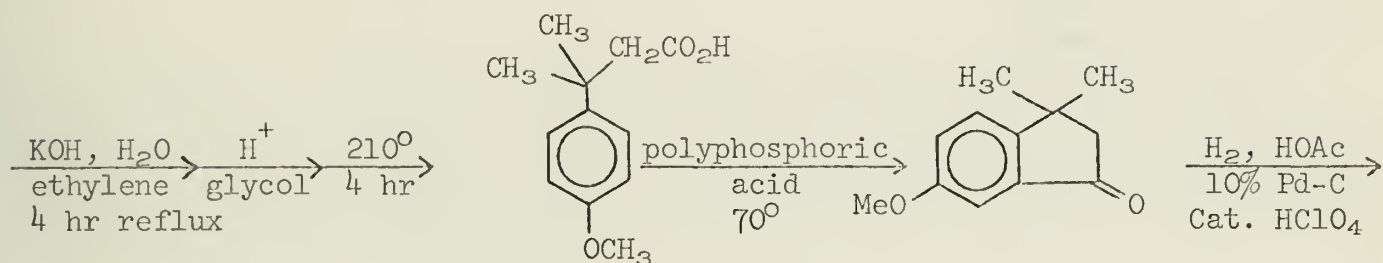
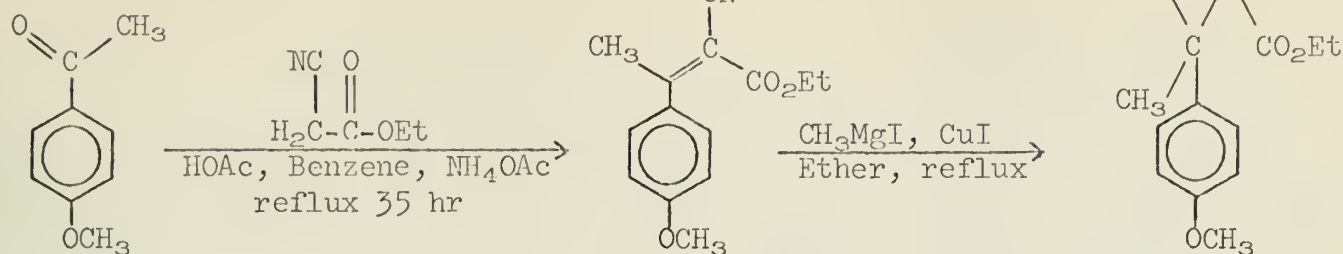
The first two examples (clovane and culmorin) demonstrate an approach to synthesis which I shall call the "traditional approach." That is, the ring systems are built up by condensing small carbon fragments to a starting compound which is usually a cyclic compound having the size of one of the rings in the final compound. These side chain fragments are then cyclized to give the desired ring system. The key to this type of synthesis is to have the condensations and subsequent cyclizations occur at the proper position and with the proper stereochemistry. This type of synthesis usually has several key steps.

In the synthesis of clovane (1)<sup>9</sup> (see Scheme 1) there are two key steps which determine the overall stereochemistry of the molecule. The first key step (conjugate addition of cyanide to 2) affords the desired cis AB ring fusion. The reaction conditions used ( $\text{KCN-EtOH/H}_2\text{O}$  reflux) caused this to be a reversible reaction and therefore the thermodynamically more stable product results. In this type of ring system the thermodynamically more favorable AB ring junction is cis. The second key reaction is the addition of a methyl group at position a in compound 3. This reaction relies on steric control, since one would expect the methyl group to approach the intermediate carbanion trans to the carboxylate group at position b.<sup>10</sup> This reaction would then put the two carboxylate groups in the desired cis relationship. The desired product was obtained as shown by the ready conversion of the diacid of 4 into its anhydride. Ring C was then completed by using a reaction sequence that had been previously used in the synthesis of cedrol.<sup>10</sup>

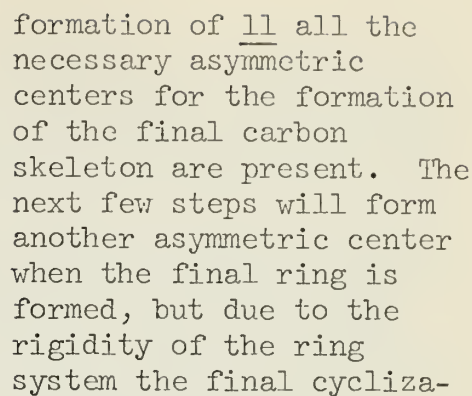


The synthesis of culmorin (5)<sup>12</sup> can also be viewed as having two key steps (see Scheme 2), the first key step being the cyclization of 8. Besides the desired [4.2.1] bicyclo system (9), another possible product could have been the [5.1.0] bicyclo system (6). However, this would involve formation of a strained system and was therefore considered unlikely. Formation of 9 in good yield showed that this argument was indeed valid. As a result of this step, two of the rings have been formed, and all four of the methyl groups are now in the proper position. The other key step involves addition of a two carbon fragment to compound 10 in the exo orientation at carbon a. There is much precedent for exo attack in the simpler bicyclo [2.2.1] systems,<sup>13</sup> and 'the rule of exo attack' should apply in this case since the geometry around the reacting center (see structure 7) is similar to that in the bicyclo [2.2.1] systems. Again the desired compound (11) was formed. With the



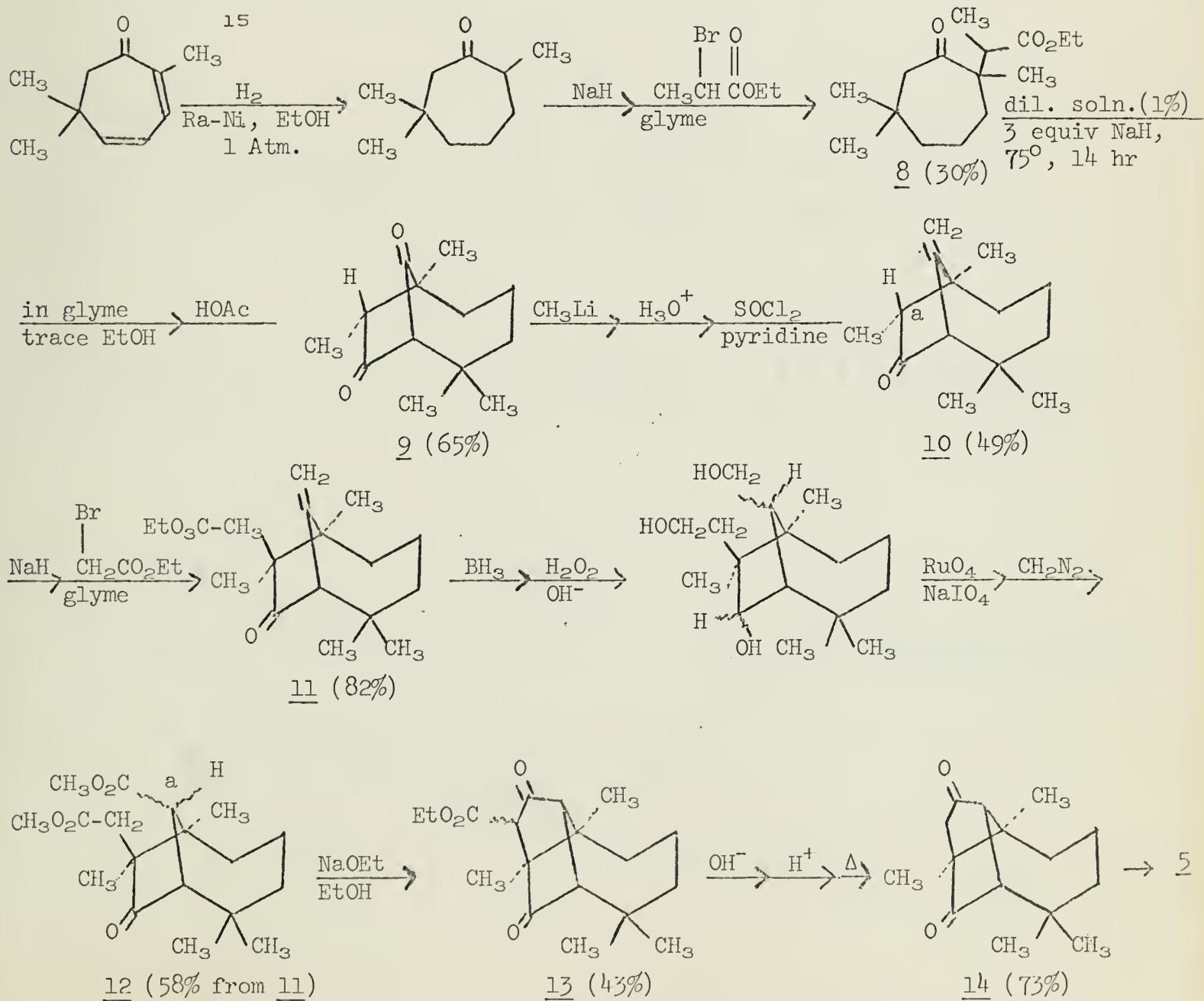






tion to give 13 can only occur in the desired direction. Also, the reaction conditions to form 13 (sodium ethoxide in ethanol) will cause equilibration about carbon a in 12, so the isolation of the desired stereoisomer of 12 would have been fruitless. Although reduction of 14 could give as many as four possible products, it had previously been found that the reduction of 14 by sodium in 1-propanol gave culmorin as 60% of the product.<sup>14</sup>

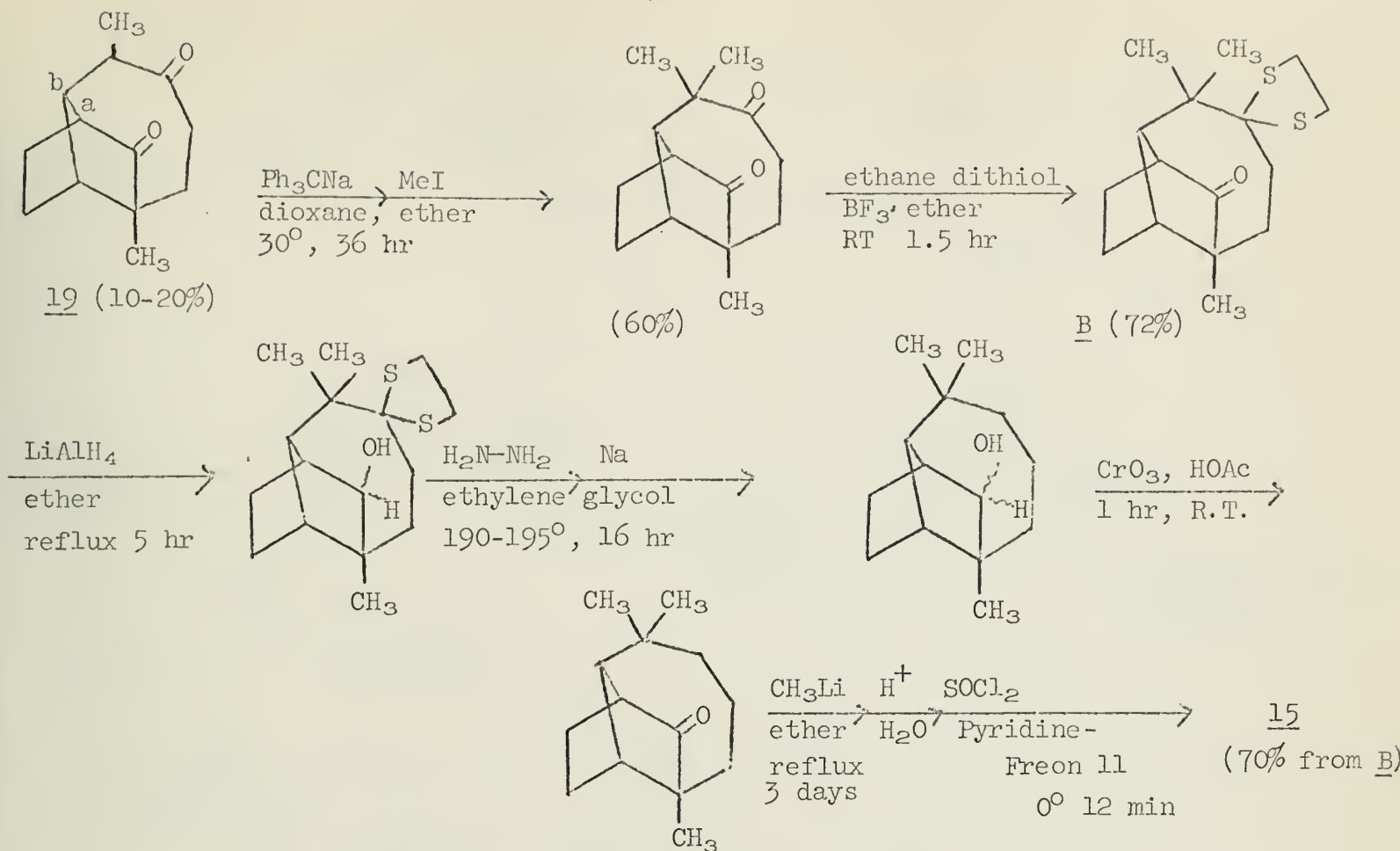
Scheme 2





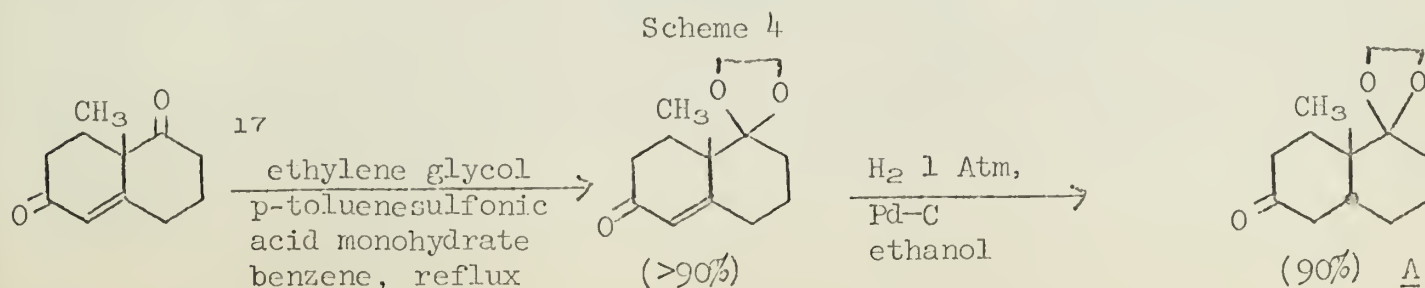




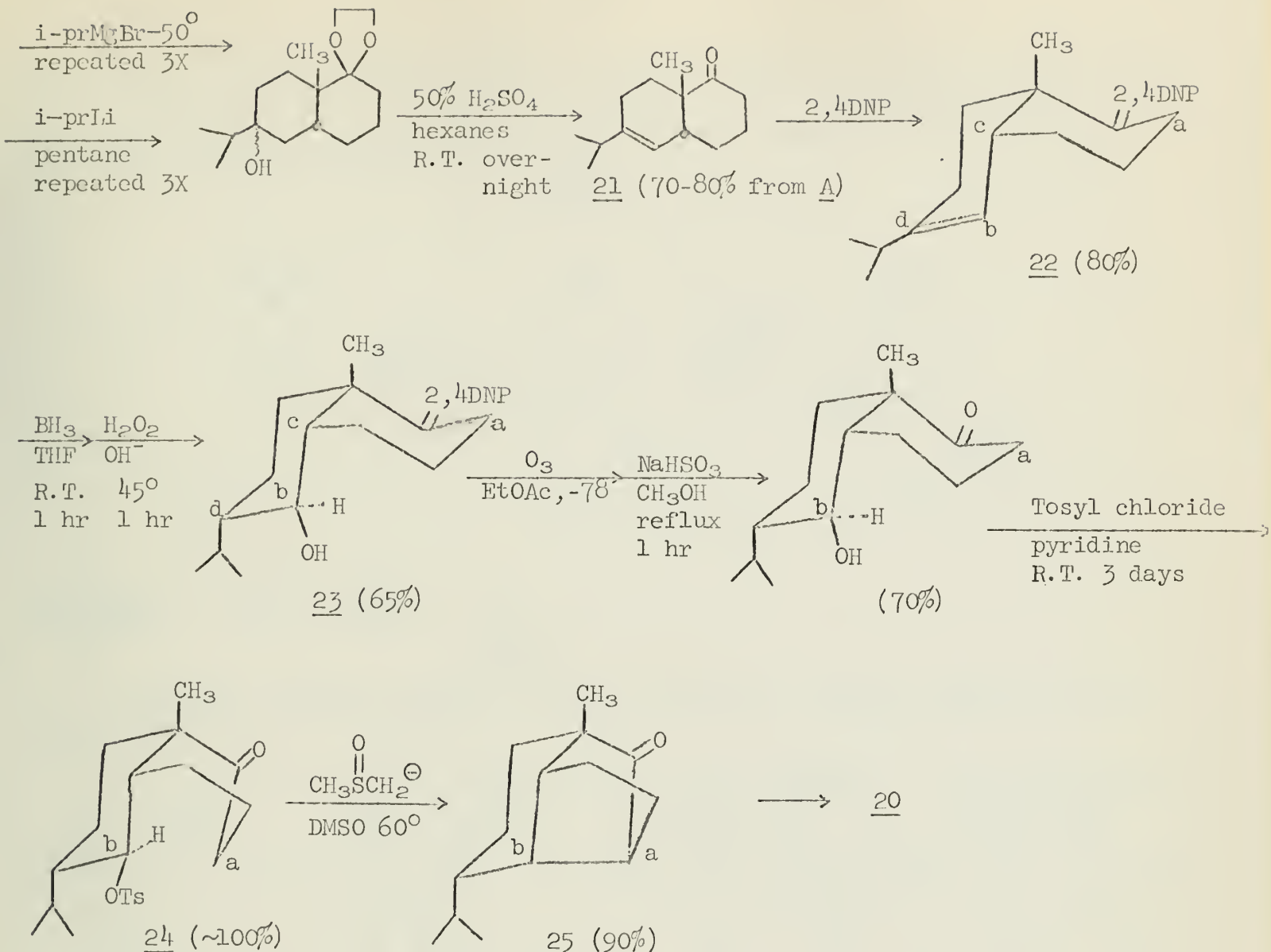


The synthesis of sativene (20)<sup>18</sup> (see Scheme 4) has as its key step bond formation between positions a and b of 24. Again, before this key step could be carried out the fused ring system had to be modified to the proper stereochemistry. Compound 23 was prepared by the hydroboration of 22 followed by oxidation of the resulting alkylborane to the alcohol. This reaction was chosen because hydroborane undergoes cis addition to double bonds from the least hindered direction to give alcohols (after oxidation) corresponding to anti-Markovnikov addition. This should (and did) give compound 23 with the hydroxyl group being cis to the hydrogens at c and d. The desired stereochemistry was therefore achieved by steric control. Hydroboration was carried out on the 2,4-dinitrophenylhydrazine (2,4-DNP) derivative of 21 since formation of the ketal caused isomerization of the double bond and direct hydroboration of 21 reduced the keto group.

Removal of the 2,4-DNP protecting group and formation of the tosylate gave the desired key intermediate (24). Compound 24 was then treated with dimethylsulfinyl carbanion<sup>19</sup> (a strong base formed by the reaction of sodium hydride with dimethylsulfoxide) to form the desired carbon skeleton (25). Formation of sativene from 25 now required only methylation (methyl lithium in ether) and dehydration of the resulting tertiary alcohol with thionyl chloride in pyridine.



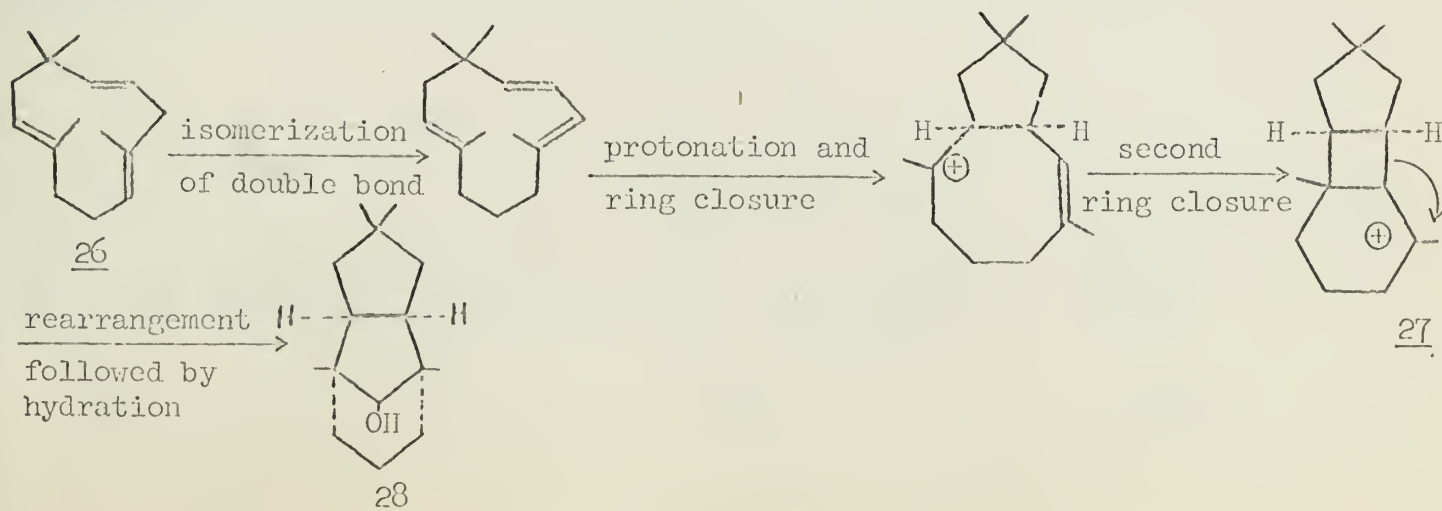




### THE CARBANION ION APPROACH

All of the above examples used carbanions in the key steps of the reaction sequence. The last two examples, however, demonstrate the use of carbonium ions in the key steps. Carbonium ions have been proposed as the key intermediates in most biosyntheses and are known to be involved in the formation of many rearrangement products of natural products. Therefore, the use of carbonium ions is in a sense paralleling nature. Again, as with the last two examples, the key intermediates must first be prepared with the proper stereochemistry.

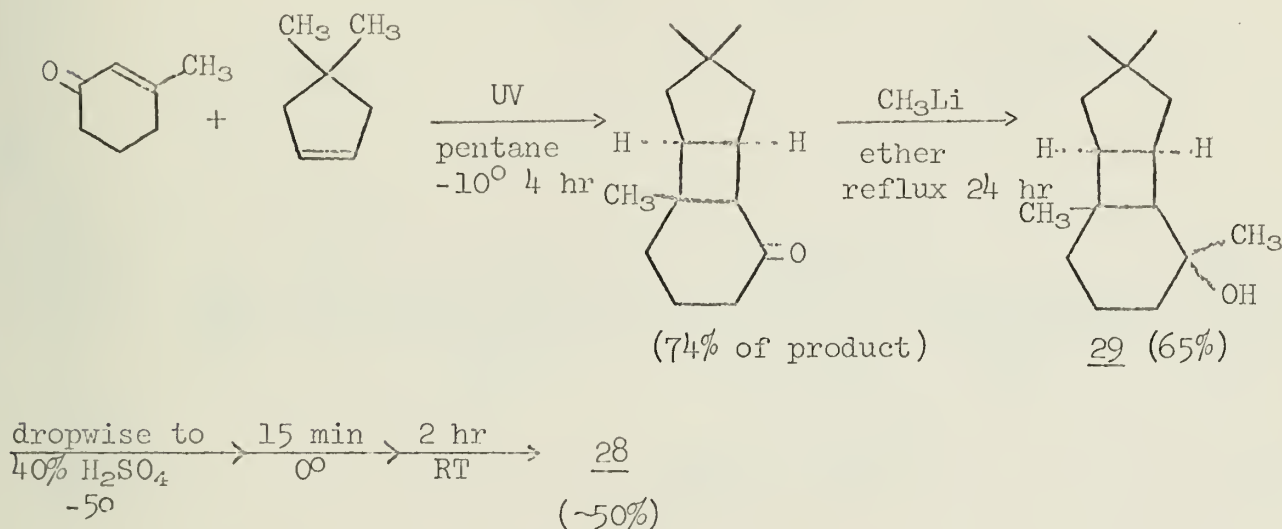
$\alpha$ -Caryophyllene alcohol (28) has been shown to arise from the acid catalyzed rearrangement of humulene (26).<sup>20</sup> Corey postulated the mechanism of this reaction to be:<sup>21,22</sup>



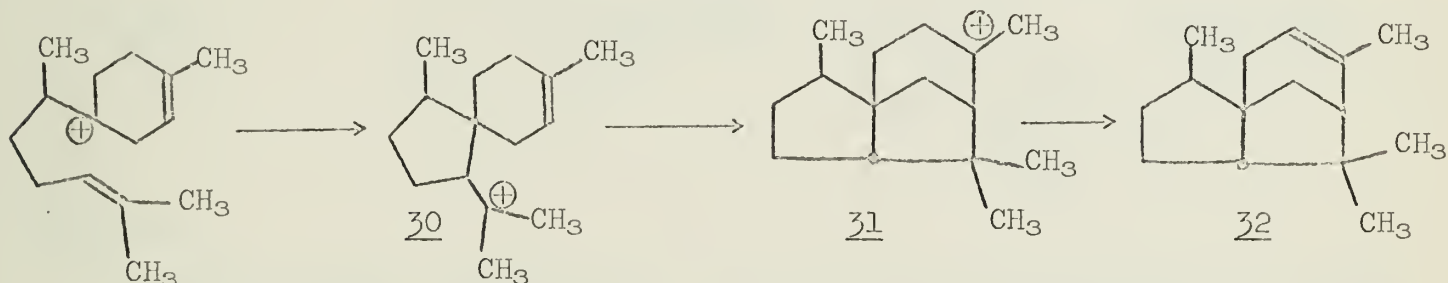


The synthesis of 28 was accomplished by preparing the key compound (29) (see Scheme 5) by a simple two-step reaction sequence, and then forming intermediate 27 by treating 29 with acid. As predicted, 28 was formed. This example shows that the use of carbonium ions can be a very elegant method of synthesis when there is a convenient route to the key intermediate.

Scheme 5

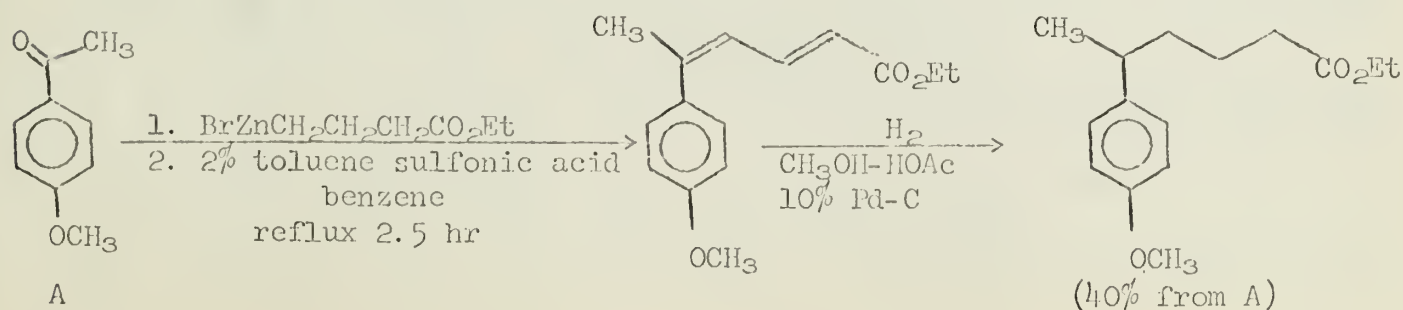


A proposed biogenetic pathway for the formation of cedrene (32) has as its final steps:<sup>23</sup>

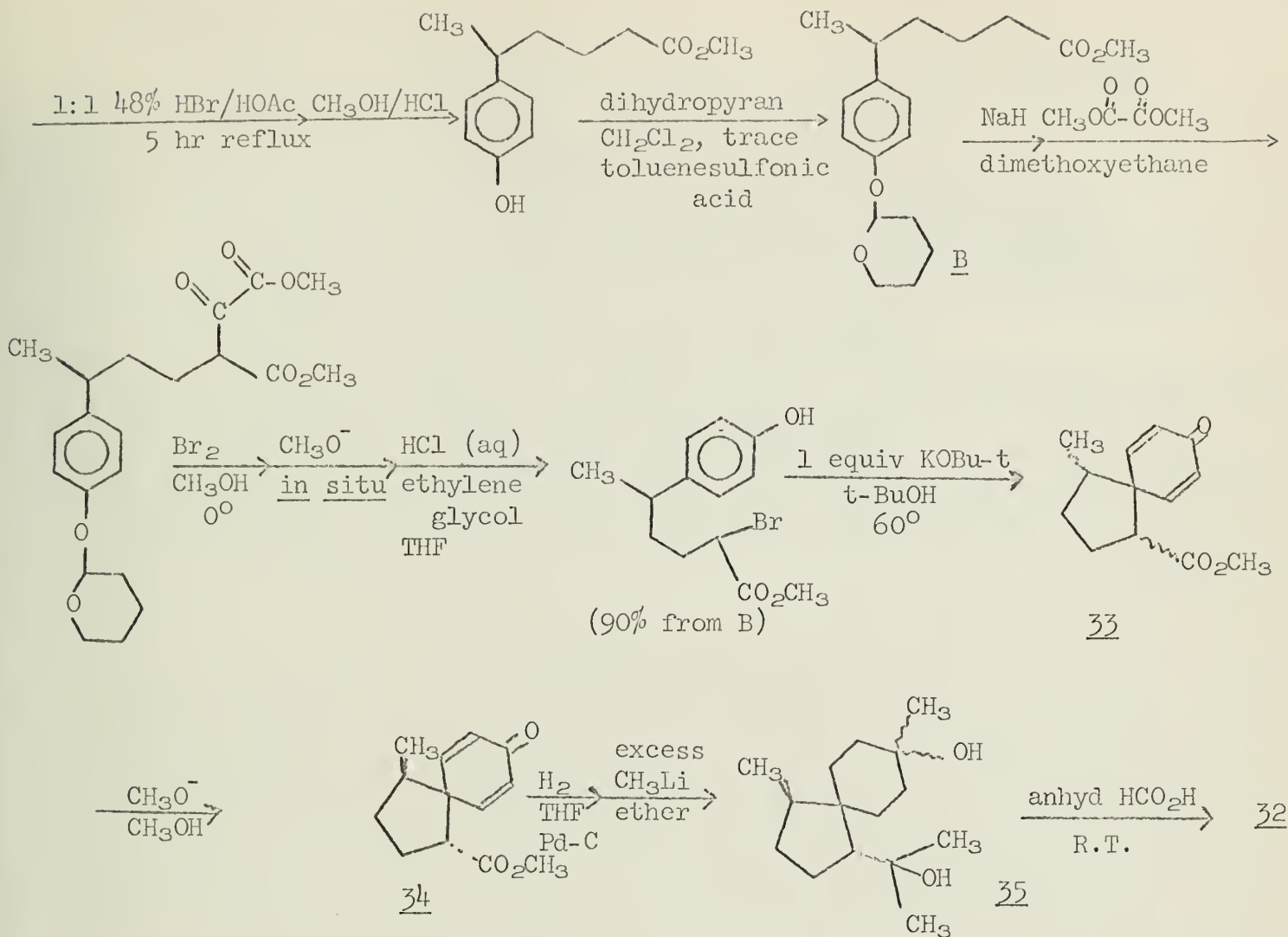


The key step in the synthesis of cedrene<sup>6</sup> (see Scheme 6) was the formation of carbonium ion 30 from compound 35. Compound 35 had in turn been prepared by the fairly straightforward reaction sequence given. The cyclization to give 33 was the only unusual reaction. However, analogous reactions of model compounds had been thoroughly studied by Winstein<sup>24</sup> and others while studying 5-phenyl participation. The equilibration to 34 was the only step involving the establishment of asymmetric centers. Since 34 is the thermodynamically more stable configuration, it was formed almost exclusively in the reaction. Treatment of 35 with anhydrous formic acid did give 32, suggesting that intermediates 30 and 31 are probably involved in the formation of cedrene.

Scheme 6







## CONCLUSION

The above examples demonstrate a few of the approaches which can be taken in the synthesis of bridged tricyclic sesquiterpenes. Each approach has its advantages and disadvantages. The traditional approach is very general, and can be used in almost any synthesis, but it usually involves more steps than the other approaches. The fused ring approach is very elegant in some cases, but it is somewhat limited as to the types of carbon skeletons and the position of substitution on the carbon skeletons to which it can be applied. The final approach is also quite elegant and offers a fairly direct route to compounds whose proposed intermediates can be easily obtained. However, if the proposed intermediates are quite complex, it may be easier to perform the entire syntheses by alternate methods. Which approach is actually used in a synthesis will be determined by the structure of the compound to be synthesized and the preference of the individual researcher.

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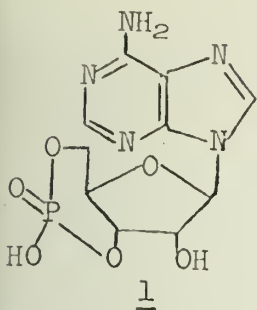


planning a synthesis.

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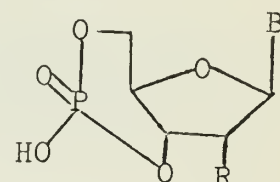
# INTRODUCTION



A "heat-stable factor" apparently acting as mediator in the function of epinephrine and glucagon in liver extracts was described in 1957 by E. W. Sutherland and T. W. Rall.<sup>1,2</sup> In the same year W. H. Cook, D. Lipkin, and R. Markham, by the reaction of aqueous barium hydroxide with adenosine triphosphate, obtained a compound chemically and physically identical to the "heat-stable factor,"<sup>2,3</sup> and later identified it as adenosine-3',5' cyclic phosphate (1).<sup>4</sup> Cyclic 3',5'-AMP has subsequently been found to participate in numerous biological processes.<sup>5-21</sup>

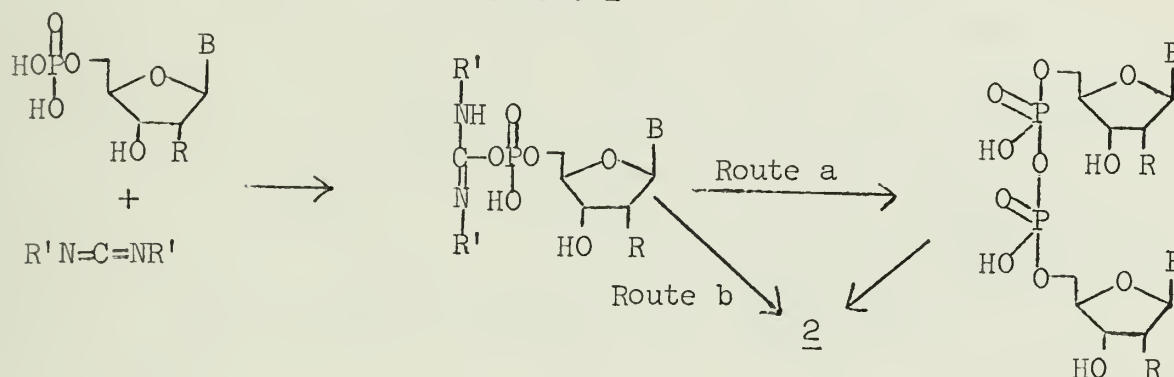
# SYNTHESIS

Cyclic 3',5'-AMP and other nucleoside-3',5' cyclic phosphates (2) have been synthesized by two principal methods. The first, developed by H. G. Khorana and others,<sup>22-26</sup> involves the carbodiimide-induced cyclization of nucleoside-5' monophosphates. Scheme I indicates the two possible routes proposed for the cyclization. A patented process<sup>27</sup> employing cyclohexyl isocyanate presumably is related to Route b.



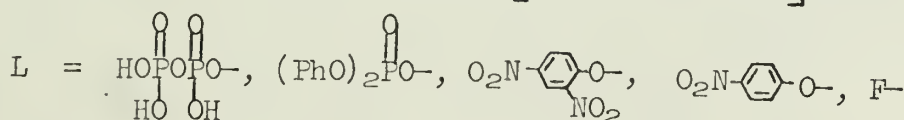
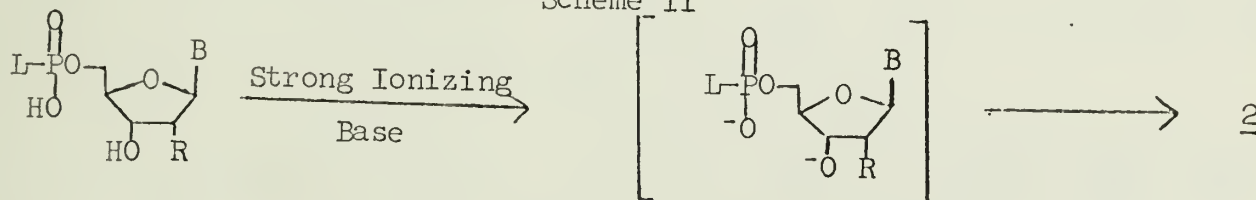
2: B = a purine or a pyrimidine  
R = H or OH

Scheme I



The second general approach<sup>3,28-31</sup> involves formation of an anionic sugar hydroxyl group which acts as the dominant nucleophile, displacing an appropriate leaving group from the phosphate function (Scheme II). The barium hydroxide synthesis<sup>3</sup> presumably operates by this general mechanism, with pyrophosphate being displaced from ATP. R. K. Borden and M. Smith used a strong ionizing base (such as *t*-butoxide) in a non-protic organic solvent (such as DMSO) to induce cyclization according to Scheme II.<sup>29-31</sup>

Scheme II



R = H or OH

# HYDROLYSIS

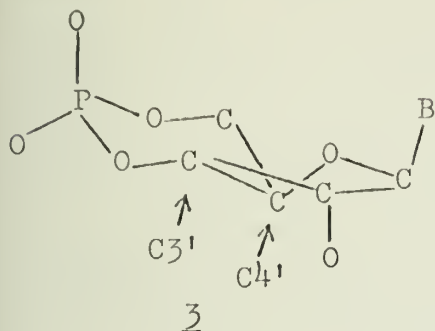
Acidic hydrolysis of 3',5'-cyclic ribonucleotides and deoxyribonucleotides demonstrate the following general trend: purine glycosidic bonds are typically stabilized and pyrimidine glycosidic bonds are typically labilized relative to the corresponding non-cyclic nucleotides.<sup>22,25,26</sup>

Aqueous sodium hydroxide, in general, causes release of free purine and pyrimidine bases from the cyclic nucleotides, but with some degradation of the chromophores.<sup>25</sup>



A specific cyclic 3',5'-nucleotide phosphodiesterase known to catalyze hydrolysis of cyclic 3',5'-AMP to 5'-AMP also catalyzes hydrolysis of other purine cyclic nucleotides, though at slower rates. Pyrimidine cyclic nucleotides, on the other hand, are only very slowly hydrolyzed by the enzyme.<sup>25,26</sup>

# CONFORMATIONAL STUDIES



Proton magnetic resonance, optical rotatory dispersion, and X-ray diffraction techniques have produced conformational information regarding several nucleoside-3',5' cyclic phosphates. The pmr<sup>32</sup> and X-ray<sup>34,35</sup> studies indicated a distortion of the ribose ring from the "best" four-atom plane to a C3'-endo (or "up")/C4'-exo (or "down") conformation (3).

Optical rotatory dispersion and X-ray data were used to determine configurations about the glycosidic bond for adenine in solution<sup>33</sup> and in the crystal<sup>34</sup> and for uracil in the crystal.<sup>35</sup>

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## AZIRIDINONES AND DIAZIRIDINONES

Reported by Gordon G. Maynes

October 27, 1969

## INTRODUCTION

The first synthesis of a 2,3-diazocyclopropanone (diaziridinone) was reported in a communication in 1964.<sup>1</sup> No further mention was made of this heterocycle until 1969, when a series of articles was published discussing the synthesis, properties, and reactions of a number of diaziridinones.<sup>2-4</sup> A series of related compounds, the aziridinones ( $\alpha$ -lactams) has been reviewed;<sup>5,6</sup> however, several papers presenting new aspects of their chemistry have been published subsequently. The purpose of this seminar is to compare the chemistry of these two series of compounds. It will not, however, provide an exhaustive review of the chemistry of  $\alpha$ -lactams before 1968.

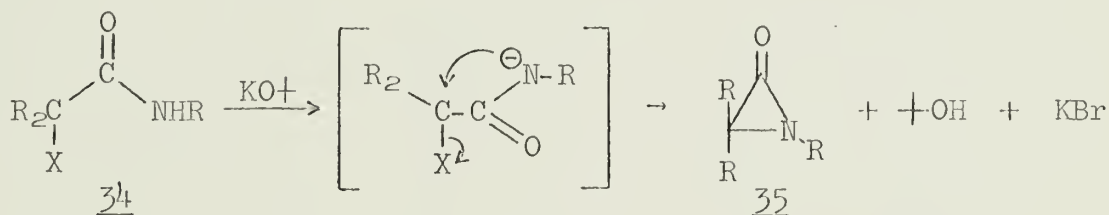
Aziridinones and diaziridinones which have been isolated as pure solids or liquids are listed in tables I and II; table III is a listing of data on those  $\alpha$ -lactams which have only been observed spectroscopically in solution.

The numbering system which will be used in this seminar is as follows:



Both aziridinones<sup>5</sup> and diaziridinones<sup>1,2</sup> may be synthesized using a procedure formally analogous to the Favorskii rearrangement. For the former, the starting material is either an  $\alpha$ -halo or an N-halo amide; for the latter, either a substituted N-halo urea or a 2,3-dialkyl carbazyl chloride. In both cases, the reaction is affected by the addition of a solution of potassium *t*-butoxide in diethyl ether to a cooled solution of the amide in the same solvent; for some N-halo ureas, potassium in pentane has been used successfully. In cases where the N-halo amide is non-isolable, it has been possible to generate it *in situ* by the addition of potassium *t*-butoxide to a solution of the amide and *t*-butyl hypochlorite in toluene<sup>8</sup> or benzene.<sup>9</sup>

The mechanism of the  $\alpha$ -halo amide-aziridinone synthesis has been suggested<sup>7</sup> to involve abstraction of the proton bonded to nitrogen, followed by intramolecular displacement of the halide, in analogy to the mechanism of the Favorskii rearrangement.<sup>23,24</sup> An analogous mechanism can be visualized for the synthesis of diaziridinones from N-halo ureas.



Most of the work on  $\alpha$ -lactams has been reported in communications, resulting in a paucity of experimental data. Sheehan and Lengyel<sup>7</sup> published an article in which they reported the isolation of the aziridinone and starting material when the reaction was run at  $-25^{\circ}$ , but only account for 71% of the starting material. Although no authors have achieved good mass balance, Bott<sup>14</sup> did report the isolation and identification of secondary products, in this case, an isocyanide and an aldehyde. Sheehan and Benson<sup>12</sup> synthesized di-*t*-butyl aziridinone 4 by the addition of dichlorocarbene to an imine 36, followed by hydrolysis of the *gem*-dichloride to the carbonyl group. This method is not general, as evidenced by the hydrolysis of several dichloro-



Table I

No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	mp	bp	C=O str.	$\lambda_{\text{max}}$	ref.
1.	<u>t</u> -butyl	methyl	methyl	22-4°	--	1837 cm <sup>-1</sup>	--	7
2.	"	phenyl	H	32-3°	--	1847 cm <sup>-1</sup>	--	8,9
3.	"		phenyl	79-81°	--	1847 cm <sup>-1</sup>	--	10,11
4.	"	<u>t</u> -butyl	H	--	38°(0.4 mm)	1835 cm <sup>-1</sup>	251 nm <sup>a,b</sup>	12
5.	l-adamantyl	l-adamantyl	H	180°		1830 cm <sup>-1</sup>	252 nm <sup>a,c</sup>	13
6.	<u>t</u> -butyl	methylcyclopentyl	H	--	72-3°(0.4 mm)	1835 cm <sup>-1</sup>	246 nm <sup>a</sup>	11
7.	"	methylcyclohexyl	H	--	81.2(0.35 mm)	1835 cm <sup>-1</sup>	247 nm <sup>a</sup>	11
8.	"	3,5,7-trimethyl-l-adamantyl	H	--	--	--	--	14
9.	"	l-adamantyl	H	--	--	--	252 nm <sup>a,c</sup>	14
10.	"	spiro-cyclohexyl		<25°	--	1835 cm <sup>-1</sup>	--	15
11.	"	spiro-adamantyl		"	--	--	--	16
12.	l-adamantyl	spiro-adamantyl		d	--	--	--	16
13.	<u>t</u> -butyl	spiro-cyclopentyl		--	--	--	--	17
14.	"	spiro-cyclooctyl		--	--	1835 cm <sup>-1</sup>	--	17
15.	"	<u>p</u> -chlorophenyl	H	35-6°	--	1830 cm <sup>-1</sup>	--	11,5
16.	"	<u>p</u> -bromophenyl	H	56-7°	--	--	--	11,5
17.	l-adamantyl	<u>t</u> -butyl	H	82-3°	--	1835 cm <sup>-1</sup>	254 nm <sup>d</sup>	18a

<sup>a</sup>In hexane. <sup>b</sup>Ref. 11. <sup>c</sup>Ref. 17. <sup>d</sup>Ref. 18b.

Table II

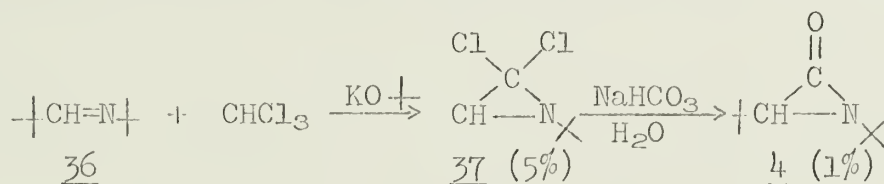
18.	<u>t</u> -butyl	H	H	--	--	1843 cm <sup>-1</sup>	--	8
19.	"	methyl	H	--	--	1840 cm <sup>-1</sup>	--	7
20.	<u>n</u> -propyl	"	H	--	--	1840 cm <sup>-1</sup>	--	7
21.	<u>i</u> -propyl	phenyl	H	--	--	--	--	11,5
22.	cyclohexyl	phenyl	H	--	--	--	--	11,5



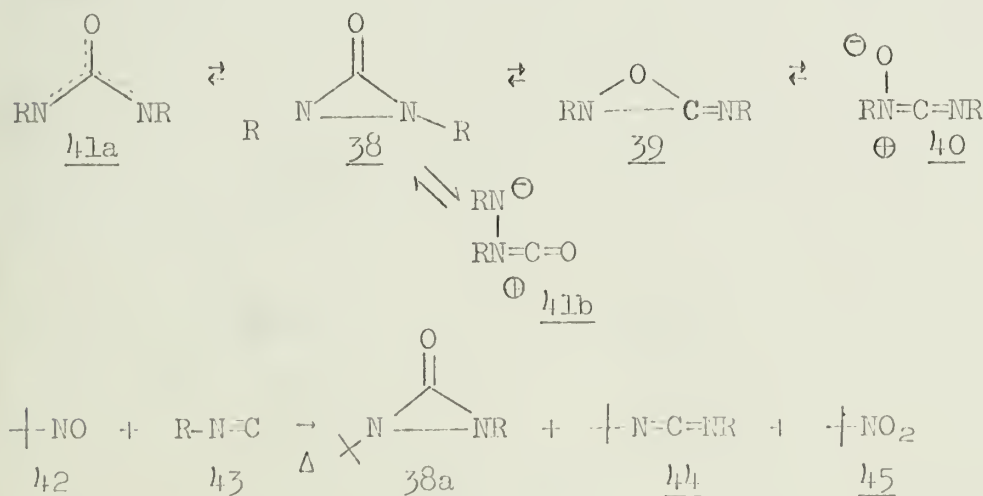
Table III

No.	R <sub>1</sub>	R <sub>2</sub>	mp	bp	C=O str	λ <sub>max</sub>	ref
23.	<u>t</u> -butyl	<u>t</u> -butyl	0-1°	--	1880 cm <sup>-1</sup>	215 nm	1,2
24.	<u>t</u> -amyl	<u>t</u> -amyl	--	66.5-67.5 (8 mm)	1862 cm <sup>-1</sup>	--	2
25.	2-methyl-3-phenyl-2-propyl	2-methyl-3-phenyl-2-propyl	43-4°	--	1860 cm <sup>-1</sup>	--	2
26.	<u>t</u> -octyl	<u>t</u> -octyl	--	--	1870 cm <sup>-1</sup>	--	2
27.	<u>t</u> -butyl	<u>t</u> -octyl	--	50-50.5 (0.1 mm)	1855 cm <sup>-1</sup>	--	2
28.	<u>t</u> -butyl	2-methyl-3-phenyl-2-propyl	--	86-92° (0.02 mm)	1870 cm <sup>-1</sup>	--	3
29.	<u>t</u> -butyl	<u>i</u> -propyl	--	--	1880 cm <sup>-1</sup>	--	4

aziridines to give α-chloroamides.<sup>25, 26</sup> A similar synthesis of diaziridinones, which would involve addition to an azo compound, has not yet been reported.



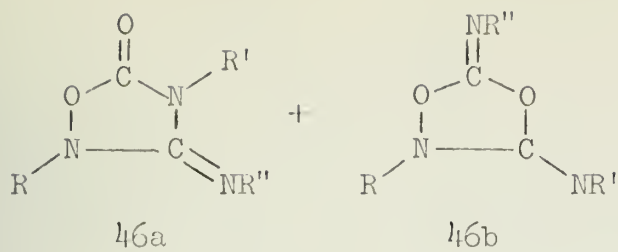
The synthesis of diaziridinones by the combination of alkyl isocyanides with nitrosoalkanes, which presently lacks an analogy in the formation of α-lactams, is based on the possibility of ring-chain isomerism in this system. (See ref 24, 27-32 for isomerizations in related systems.) If diaziridinones were the most stable isomeric form, it should be possible to synthesize 38 through the preparation of 38, 39, 40, 41a or 41b. In an attempt to synthesize 39 or 40 Greene and Pazos<sup>4</sup> treated 2-methyl-2-nitrosopropane 42 with an alkyl isocyanide 43 to yield 38a, carbodiimide



44, and nitroalkane 45. In an attempt to elucidate the mechanism of this reaction, 42 and 43 were mixed in the presence of the 1,3-dipolarophile phenyl isocyanate.<sup>33, 34</sup> This trapping agent was shown to be inert to the products under the reaction conditions, and to have little or no effect on the overall rate of the reactions.

However, in place of the previously observed products, a series of 1:1:1 adducts was obtained, which were tentatively assigned the following structures:

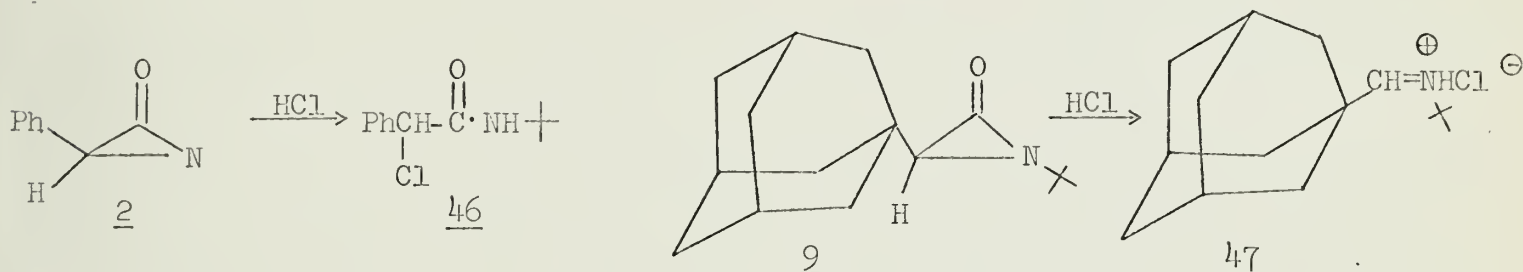




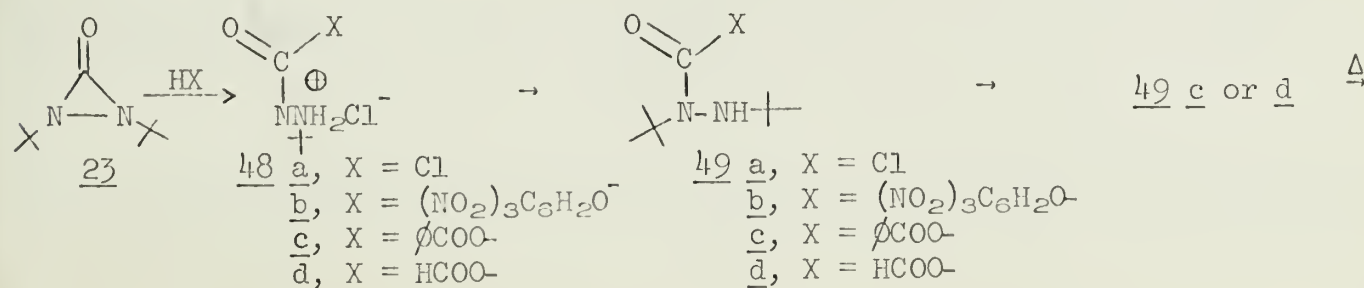
This evidence excludes any formation of products from direct bi- or termolecular reactions, and argues strongly for an intermediate. The carbodiimide N-oxide 40 is a favored structure on the basis of the reactivity of the intermediate toward 1,3-dipolarophiles. Structure 39 can not be ruled out, but, in comparison to nitron and oxaziridine reactivity,<sup>33</sup> it appears unlikely.

That aziridinones exist as structure 38, as opposed to one of the other possible isomers has been elucidated and reviewed in the past.<sup>6</sup> That diaziridinones have the analogous localized structure was suggested in 1969 by Greene and co-workers.<sup>2</sup> They based their assignment on spectral data and on reactions to be discussed subsequently. Further, they assigned the stereochemistry of the two N-alkyl groups as trans on the basis of infrared and variable temperature nuclear magnetic resonance studies.

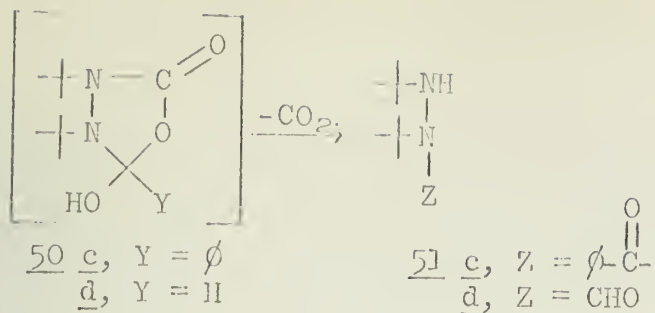
A reaction which has been studied for both series of compounds under consideration is their cleavage by acids. With aqueous or ethanolic HCl, 1-t-butyl-3-phenylaziridinone 2 opens to an N-t-butyl- $\alpha$ -chlorophenylacetamide 46,<sup>35</sup> a reaction which occurs with cleavage of the alkyl-nitrogen bond and which is formally a reversal of the synthesis. In methanol containing a trace of *p*-toluenesulfonic acid, 4 reacts in an analogous fashion to yield the  $\alpha$ -methoxyamide.<sup>12</sup> In contrast to these data, Bott<sup>14</sup> reported the reaction of 2 with a solution of HCl in diethyl ether to yield an aldimonium chloride 47. In methanol, in which 47 is unstable, the corresponding aldoximes were isolated upon treatment with hydroxylamine.



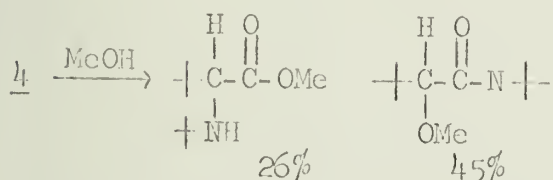
Diaziridinones, when treated with dry HCl, afford an immediate precipitate which, when treated with water, yields the carbazyl chloride 49a. The precipitate has been assigned the structure of a carbazyl chloride hydrochloride 48, rather than a protonated diaziridinone on the basis of spectroscopic evidence. (2 t-butyl singlets in the nmr, and a C=O str at 1750  $\text{cm}^{-1}$  in the infrared). Picric, benzoic and formic acids have been shown to react to yield analogous products 49b,c, and d; those from the latter lose carbon dioxide on heating to afford 51c and d. When treated with hydrochloric acid, diaziridinones decarboxylate, probably through a carboxyhydrazine intermediate formed by the effective addition of hydroxide to the carbonyl. In support of this assumption, 23 has been shown to react with methanolic sulfuric acid to yield the methyl carbazate.<sup>2</sup>



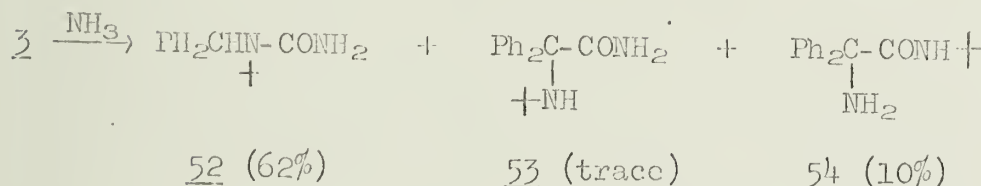




10, 13, and 14; <sup>17</sup> *t*-butylamine and phenylhydrazine with 2; <sup>32</sup> and for water, *t*-butyl alcohol, benzylamine, benzylthiol, and ethyl glycinate with 1.<sup>7</sup> In a less selective reaction, 4 reacts with MeOH slowly at reflux in the following manner:<sup>12</sup>



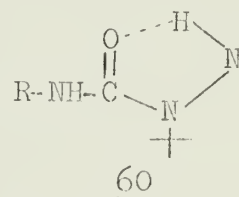
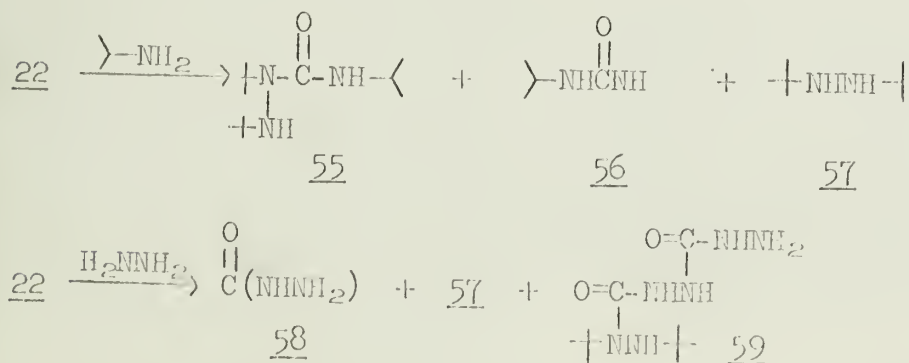
liquid ammonia, and for both 2 and 3 with a variety of amines. It is interesting



to note that treatment of 3 with *t*-butyl alcohol gives the "normal" alkyl-nitrogen cleavage product in essentially quantitative yield.

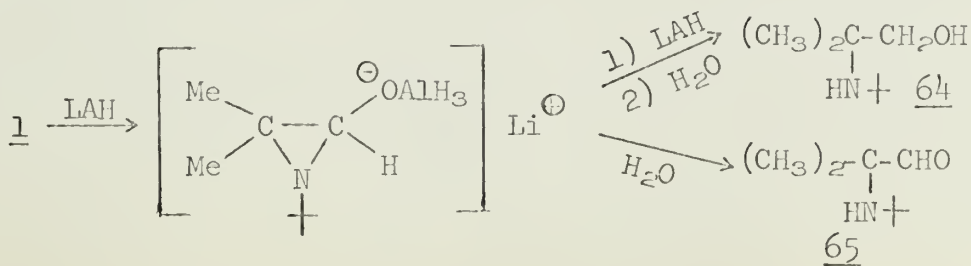
While it is tempting to suggest steric control of the reaction, it is dangerous to try to correlate data taken over such a range of conditions.

The corresponding reaction of diaziridinones has been studied for relatively few nucleophiles. A partial justification for this deficiency may be found in the competing, and often more rapid redox reaction to be discussed later. With *i*-propylamine and with hydrazine, the exclusive nucleophilic reaction is one of acyl-nitrogen cleavage. When a large excess of nucleophile is used, the yields of products 56 and 58 were enhanced at the expense of 55 and 59. When 55 is compared to the sterically similar model compound 1-*t*-butyl-3-isopropylurea, the greater reactivity of the former toward nucleophiles may be explained either by invoking intramolecular catalysis via a structure such as 60, or by postulating dissociation of 55 to isopropyl isocyanate and 1,2-di-*t*-butylhydrazine, followed by reaction of the isocyanate with isopropylamine. Secondary amines were found to be too unreactive

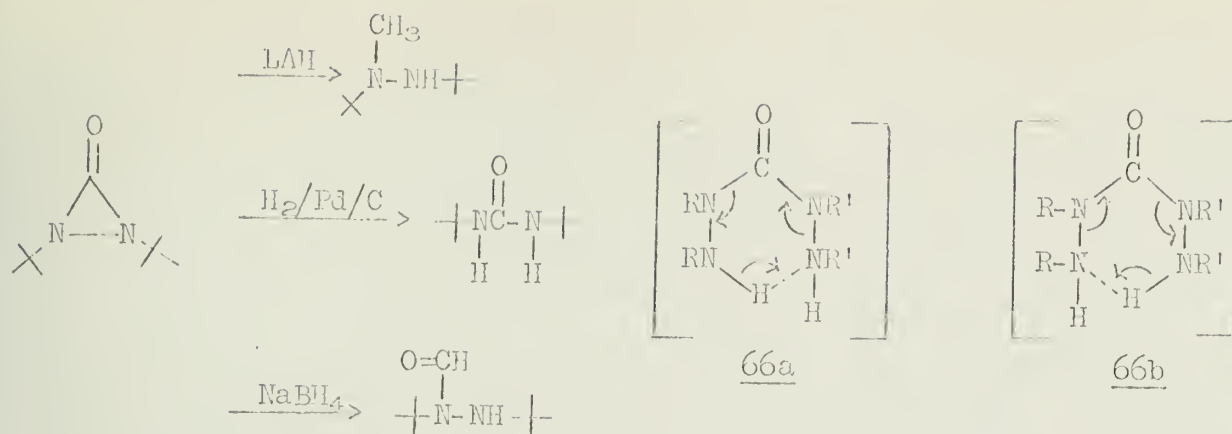


toward diaziridinones to allow a distinction to be made between the two possibilities. With *t*-butylhydroxylamine, two competing rxns are observed; a redox reaction, leading to







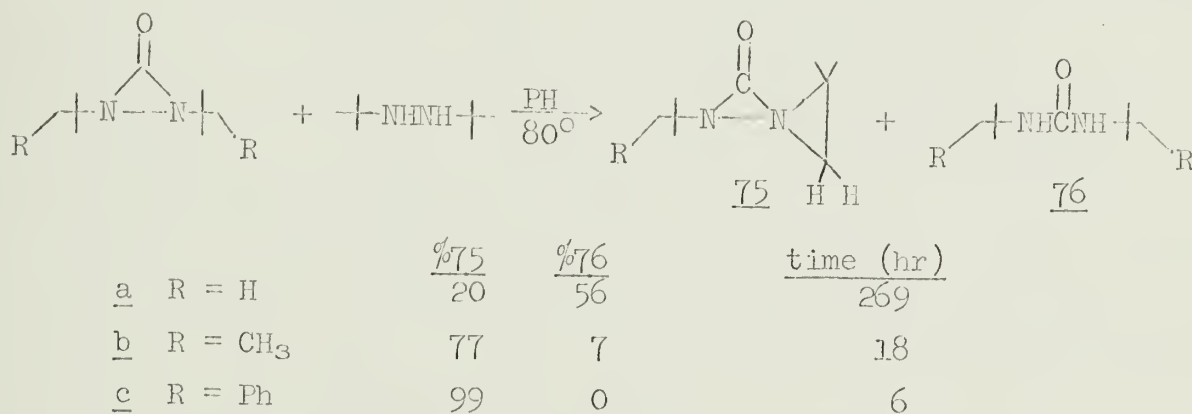


Diaziridinones, in contrast to  $\alpha$ -lactams, will also undergo redox reactions with organic reducing agents to yield N,N'-dialkyl ureas. When substituted hydrazines are used as reducing agents an isomerization side reaction is observed.

Two mechanisms for the redox reaction are, in theory, possible: nucleophilic addition of the hydrazine to the carbonyl, followed by fragmentation of the intermediate 74 by either of two paths, a or b, with ultimate recombination of the resulting isocyanate and amine, or hydrogen transfer. The distinction was made by two "crossover" experiments. The results of this study exclude the addition-fragmentation scheme.

Although no crossover occurs, a lower yield of urea was observed for 23, due to a concurrent isomerization of the starting material to an aziridinecarboxamide.

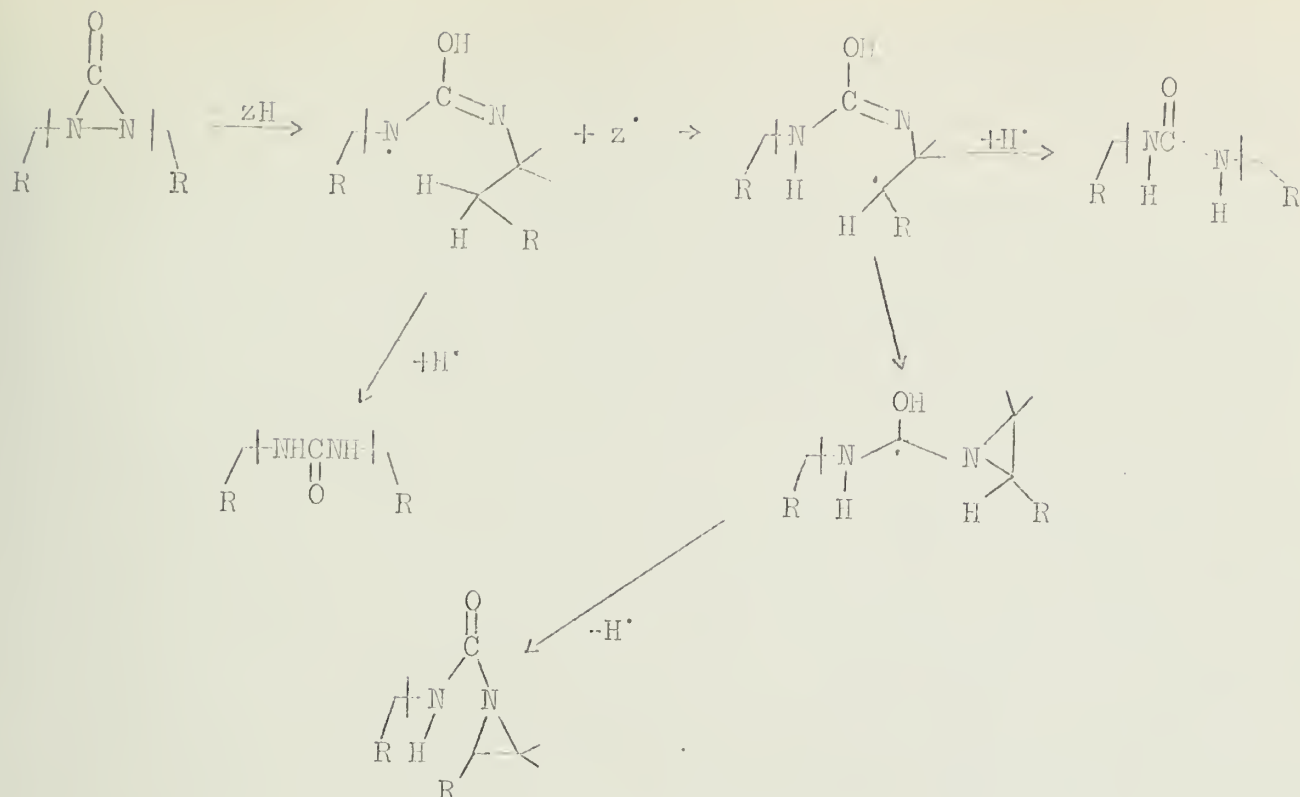
The effect of the structure of the diaziridinone was examined by the experiments in Scheme I.



That the hydrazine is a catalyst was shown by demonstrating that the diaziridinones are stable under the reaction conditions both in the absence of added substances, and in the presence of the reaction products. A concentration study showed that lower concentrations of hydrazine (down to 0.08 mole fraction) favored the isomerization reaction over the redox reaction. Of the diaziridinones considered in this study, only 25 reacts at all in the presence of tetramethylhydrazine, and its rate of isomerization with this catalyst is 50 times slower than with trimethylhydrazine. On the basis of this evidence, Greene, Pacifici and Bergmark<sup>3</sup> favor a reaction sequence in which the intramolecular hydrogen abstraction is by nitrogen rather than oxygen,<sup>42-44</sup> occurs by a six-atom transition state, and shows the proper selectivity for benzyl C-H > methylene > methyl. The resulting carbon radical is afforded only the opportunity to cyclize to the azacyclopropylcarbinyl radical.

In the reactions which are shared by all three carbonyl-containing three-membered rings, the order of reactivity is cyclopropanone >  $\alpha$ -lactam > diaziridinone which suggests that delocalization of the unshared pair(s) of electrons on the nitrogen serves to stabilize the heterocycles. It is apparent that further study of the reactions of all three compounds is required. This is especially apparent in consideration of the nucleophilic cleavages of aziridinones. Unfortunately, the fact that most of the reactions of aziridinones have been run under differing conditions prevents general mechanistic conclusions from being drawn with any certainty.





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# REACTIONS AND MECHANISMS OF NICKEL CARBONYL IN SYNTHETIC ORGANIC CHEMISTRY

Reported by Larry F. Charbonneau

November 3, 1969

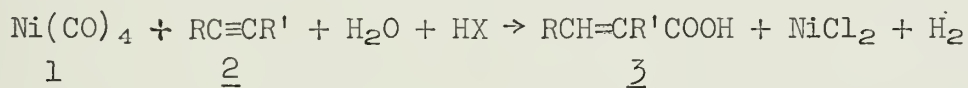
## I. INTRODUCTION

Nickel Carbonyl was first discovered by L. Mond and co-workers in 1890, but the catalytic activity of the carbonyl was not recognized<sup>1</sup> until 1939 when the German chemist W. Reppe discovered the carbonylation and cyclization reactions of acetylenes, which are catalyzed by nickel carbonyl, or by complexes derived from nickel carbonyl. After World War II, Reppe was persuaded<sup>2</sup> to make public his knowledge of acetylene chemistry and metal carbonyl catalysis. Industrial and academic laboratories then initiated studies which extended Reppe's work on carbonylation reactions and helped to develop the chemistry of  $\pi$  complexes of transition metals.<sup>1</sup> Several reviews<sup>1,3-11</sup> describing the use of metal carbonyls in organic syntheses have appeared in the past decade. A recent book<sup>12</sup> reviews the preparation, structure, and properties of the metal carbonyls and their synthetic applications in organic chemistry. This seminar will discuss recent developments in the mechanisms of nickel carbonyl reactions with organic compounds, excluding cyclopentadienyl complexes of nickel, and polymerization of acetylenes since they have been adequately discussed elsewhere.<sup>1,4,11</sup>

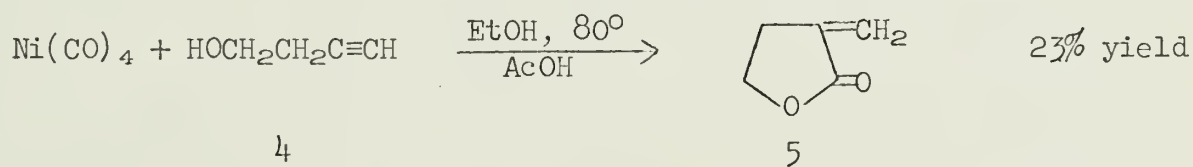
## II. CARBONYLATION OF ALKYNES

The term "carbonylation" is used by Schrauzer<sup>1</sup> and others to describe the preparation of compounds in the presence of nickel carbonyl where formally a molecule of carbon monoxide has added to substrate. Schrauzer's review<sup>1</sup> presents the following data, which must be considered in determining the carbonylation mechanism of acetylenes:

- 1) When acetylenes (2) are treated with nickel carbonyl (1) in aqueous acidic media, acrylic acids (3) are formed.

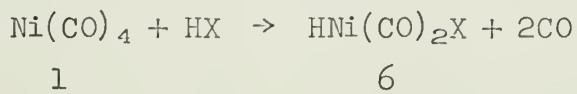


- 2) If anhydrous acids are used, hydrogenation of 3 to a propionic acid occurs.
- 3) If the carbonylation is conducted in the presence of alcohols, amines, mercaptans, or organic acids, their esters, amides, thioesters, or anhydrides are obtained respectively.
- 4) Of all the metal carbonyls, only cobalt carbonyl can fully replace nickel carbonyl.
- 5) If the reaction of diphenylacetylene with nickel carbonyl is run in inert solvents, tetraphenylcyclopentadienone is formed.
- 6) Acetylenic alcohols were found to undergo carbonylation and  $\beta,\gamma$ -acetylenic carbinols (4) were converted to  $\gamma$ -butyrolactones (5).



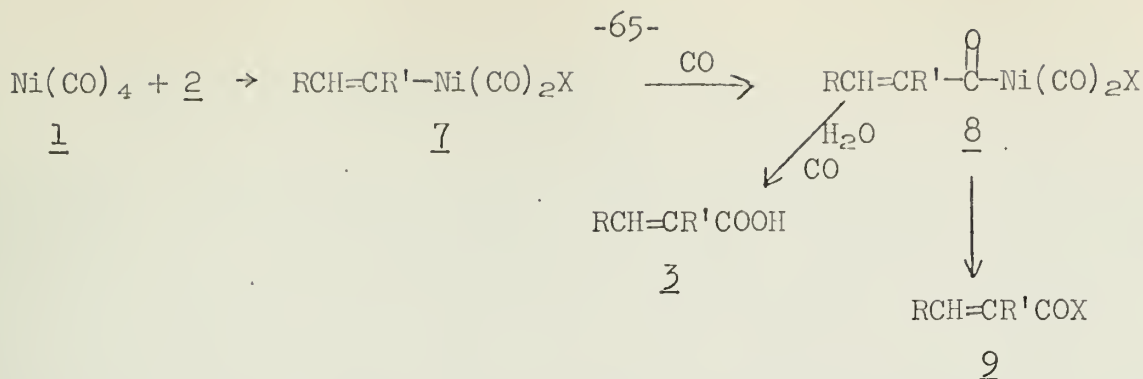
- 7) Divinyl ketones may be formed as by-products of carbonylation.
- 8) The stereochemistry of addition to the acetylenic linkage is cis.

Heck<sup>13</sup> has suggested two possible mechanisms for the carbonylation reaction. The first postulated formation of halonickel dicarbonyl hydride (6); however, no evidence for the existence of 6 has been obtained.<sup>14</sup> A second mechanism proposes that an

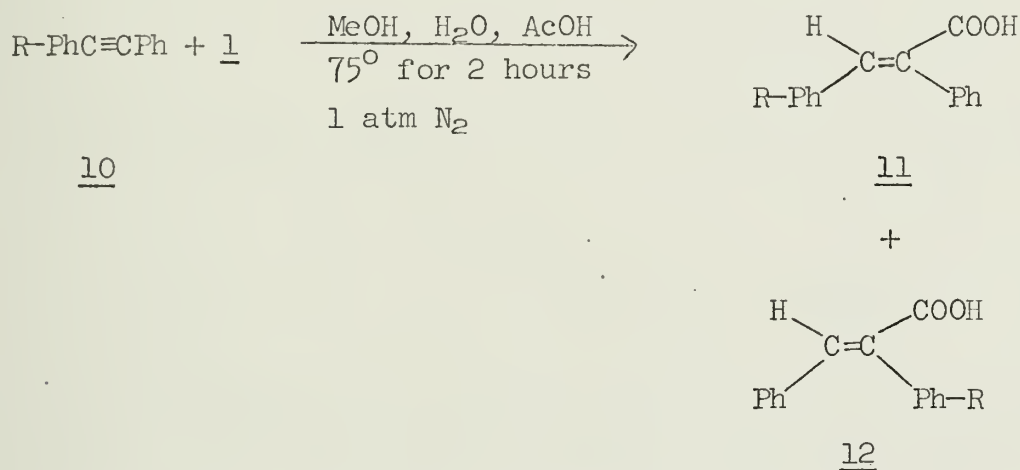


alkenylnickel dicarbonyl halide (7) forms as an intermediate during the carbonylation reaction. The reaction of 7 with carbon monoxide could give the observed products 3 and 9. The mechanisms will be discussed further after the carbonylation reactions of halides have been presented.



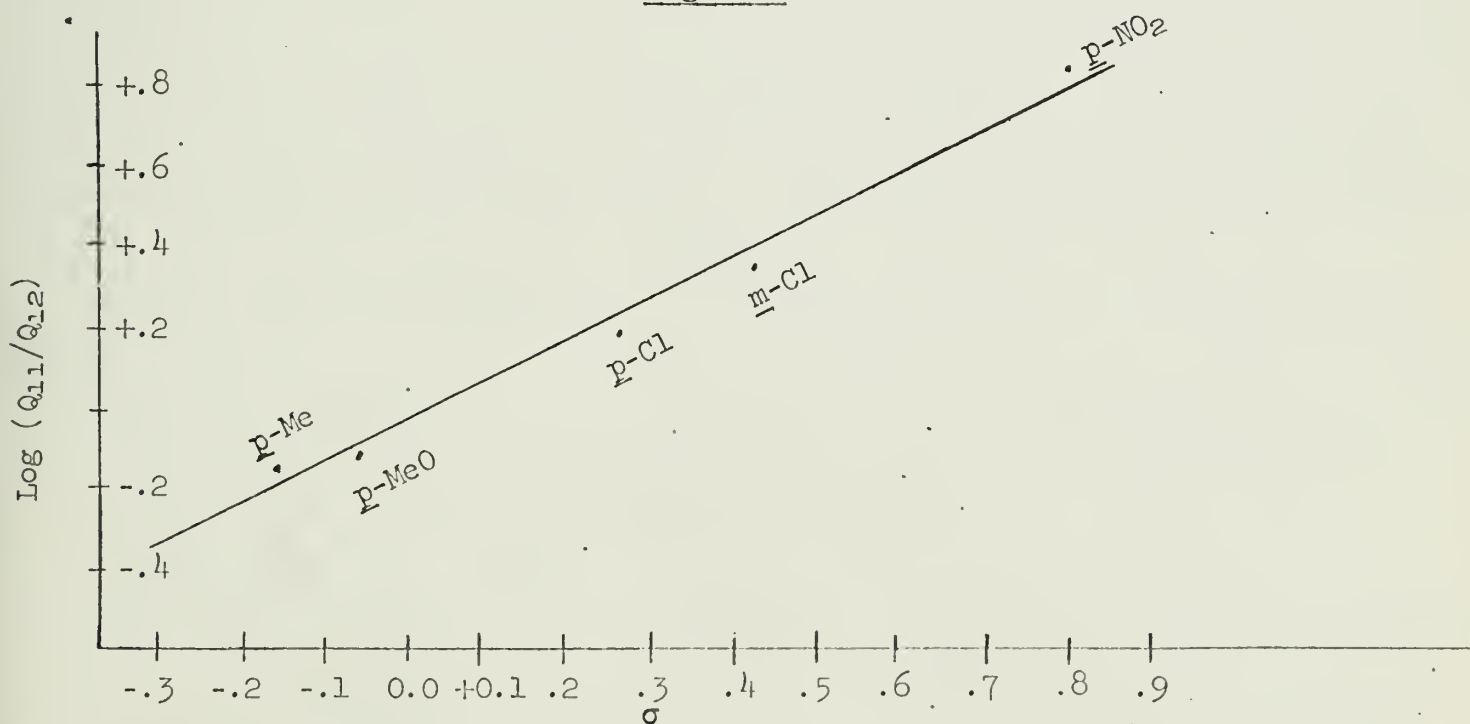


Bird and Briggs<sup>15</sup> have reported that the relative proportions of isomeric cinnamic acids 11 and 12 obtained by carbonylation of meta and para monosubstituted diphenyl acetylene (10) can be correlated with the sigma constants of the substituents.



Assuming that the rates of formation of 11 and 12 are proportional to the quantity of each acid formed ( $Q_{11}$  and  $Q_{12}$ ), a Hammet plot (Figure 1) was prepared in which  $\log (Q_{11}/Q_{12})$  was plotted versus sigma. Least squares analysis of the data gave a line from which a value of 0.9 was obtained for rho. The elements of formic acid

Figure 1



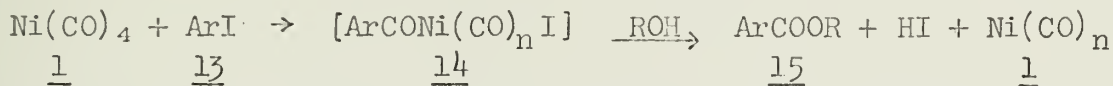
added cis to the acetylene linkage and the direction of addition of these elements in the predominant acid, obeyed the generalized Markownikoff Rule, where nickel carbonyl added to the side of the acetylenic linkage that can best support a carbonium ion. Compound 12, the product of steric control, was formed when ortho substituents were present.



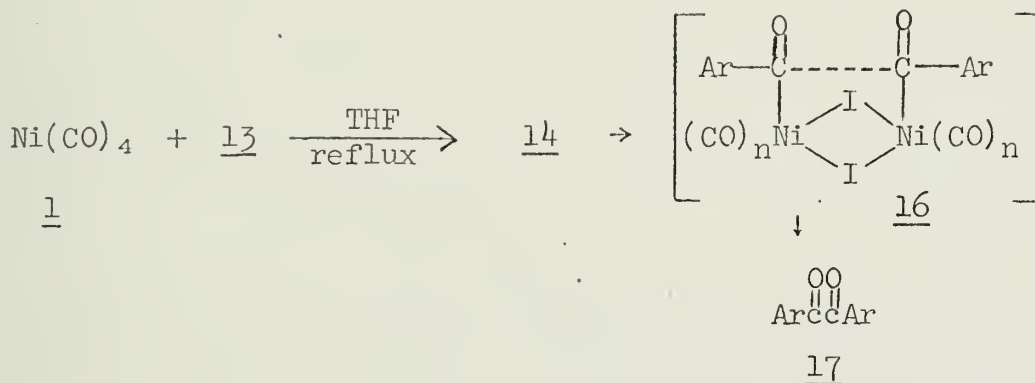
### III. CARBONYLATION OF ORGANIC HALOGEN COMPOUNDS

#### A. REACTIONS OF AROMATIC HALIDES.

Bauld<sup>16</sup> found that aryl iodides (13) are converted to esters 15 in 60-80% yields in alcoholic solvents, and to arils (17) in 10-80% yields in aprotic solvents such as tetrahydrofuran. Bauld's mechanism is analagous to Heck's second mechanism in that the

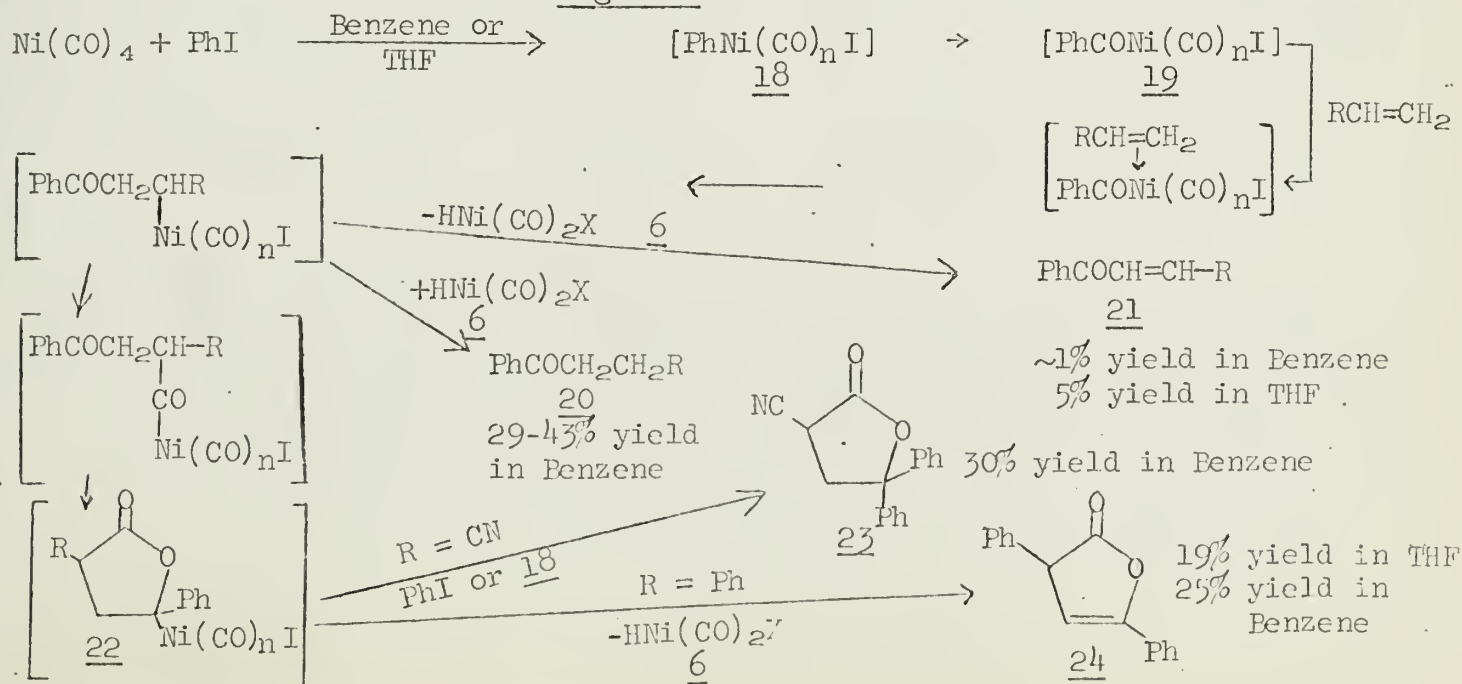


proposed intermediates 8 and 14 are similar. Aryl iodides were thought not to be intermediates because control experiments with benzoyl iodide and nickel carbonyl in tetrahydrofuran did not give benzil. The formation of arils (17) might have occurred though a transition state resembling the complex 16. Free radicals could not be



detected in reactions giving 17 when large excesses of free radical traps such as cyclohexene or benzaldehyde were present. Beckert and Lowe<sup>17</sup> believe that pentafluoriodobenzene reacts with nickel carbonyl by a free radical mechanism because the products include decafluorobiphenyl, decafluorobenzophenone, and pentafluorobenzene. No decafluorobenzil was isolated from their reactions which were run in dimethylformamide, toluene, or tetrahydrofuran. Chiusoli<sup>18</sup> and co-workers found that iodobenzene would react with acetylene in the presence of nickel carbonyl to form benzoyl propionates in high yield. Benzoyl acrylates could not be isolated, and control experiments showed that they were hydrogenated under reaction conditions. Tsutsumi<sup>19</sup> and co-workers studied the reaction of iodobenzene with nickel carbonyl in the presence of olefins such as styrene, acrylonitrile, and ethyl acrylate. The reactions were carried out in benzene or tetrahydrofuran at 50-60° for 100 hours under argon atmospheres. The author's mechanism presented in Figure 2 includes an intermediate benzoylnickel carbonylate 19 which reacts with olefin. Although the formal addition and elimination

Figure 2



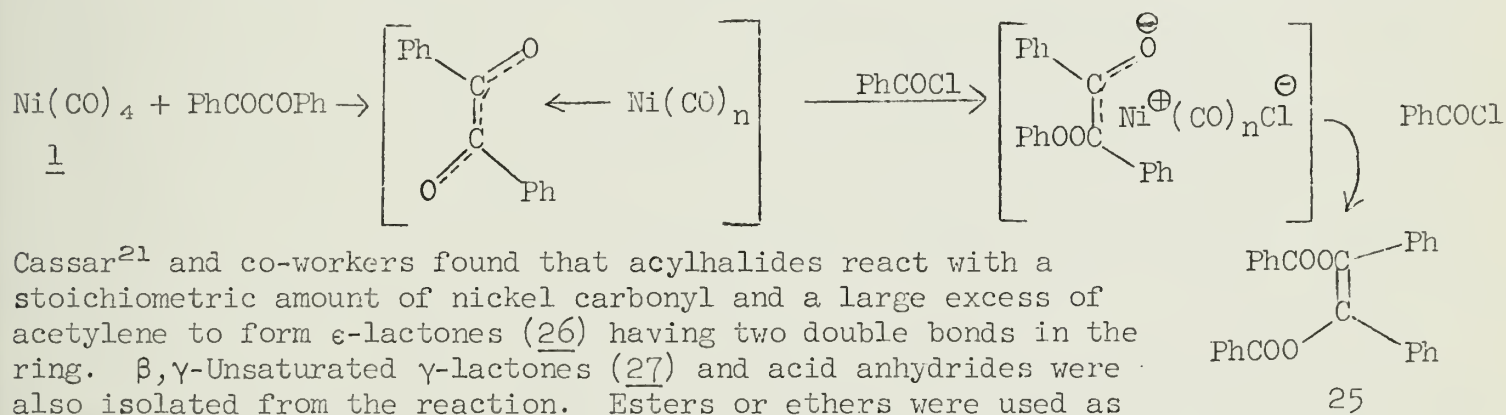


of a halonickel carbonyl hydride (6) was included in the reaction scheme there was no direct evidence given for its existence. Indirect evidence comes from the observation that in tetrahydrofuran, all the compounds isolated were unsaturated compounds such as 21, 24, and stilbene, which was isolated in 4% yield from the reaction with styrene. If the stability of an eliminated hydride complex, such as 6 is dependent on the coordinating ability of the solvent, the complex could exist in tetrahydrofuran, but it would be relatively unstable in benzene. This hypothesis was examined by adding a base such as dicyclohexylethylamine to the reaction of nickel carbonyl, iodobenzene and styrene in benzene. Only benzalacetophenone was obtained in 19% yield, and no benzylacetophenone was detected. The authors claim that the lactones isolated in these experiments were the first to be synthesized from olefins. They believe the lactones were formed by loss of 6 from the intermediate 22 if the starting olefin was styrene or by attack of iodobenzene or 18 on 22 if the starting olefin was acrylonitrile. Only ethyl (3-benzoyl)-propionate was isolated when ethyl acrylate was treated with nickel carbonyl and iodobenzene. When cyclohexene or butadiene was used as the olefin, they were recovered unreacted.

Recently Nakayama and Mizoroki<sup>20</sup> reported that arylbromides will react with nickel carbonyl to form aryl carboxylic acids if a salt such as potassium acetate is present to absorb liberated hydrogen bromide, which inhibits the carbonylation.

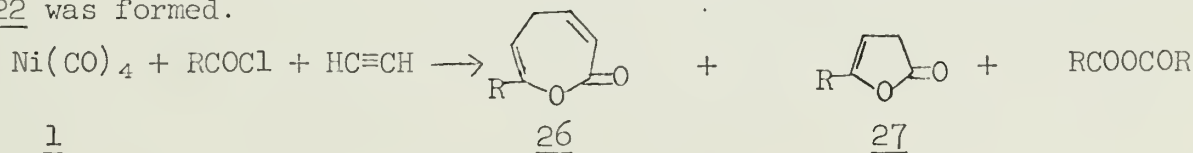
### B. REACTIONS WITH ACYLHALIDES.

Bauld<sup>16</sup> found that benzoylchloride and nickel carbonyl reacted in tetrahydrofuran to give benzil and 1,2-dibenzoyloxystilbene (25). The reaction no doubt follows a path through a complex analogous to 16 which was proposed by Bauld for the formation of arils (17) from aryl iodides (13). In a control experiment it was shown that benzil is converted to 25 in the presence of nickel carbonyl and benzoyl chloride.



Cassar<sup>21</sup> and co-workers found that acylhalides react with a stoichiometric amount of nickel carbonyl and a large excess of acetylene to form  $\epsilon$ -lactones (26) having two double bonds in the ring.  $\beta,\gamma$ -Unsaturated  $\gamma$ -lactones (27) and acid anhydrides were also isolated from the reaction. Esters or ethers were used as solvent, and the reaction was quenched with H<sub>2</sub>O. Lactone 27 is similar to lactone 24, isolated by Tsutsumi (see Figure 2), whereas lactone 26 might have occurred by the insertion of a second mole of acetylene before a complex analogous to 22 was formed.

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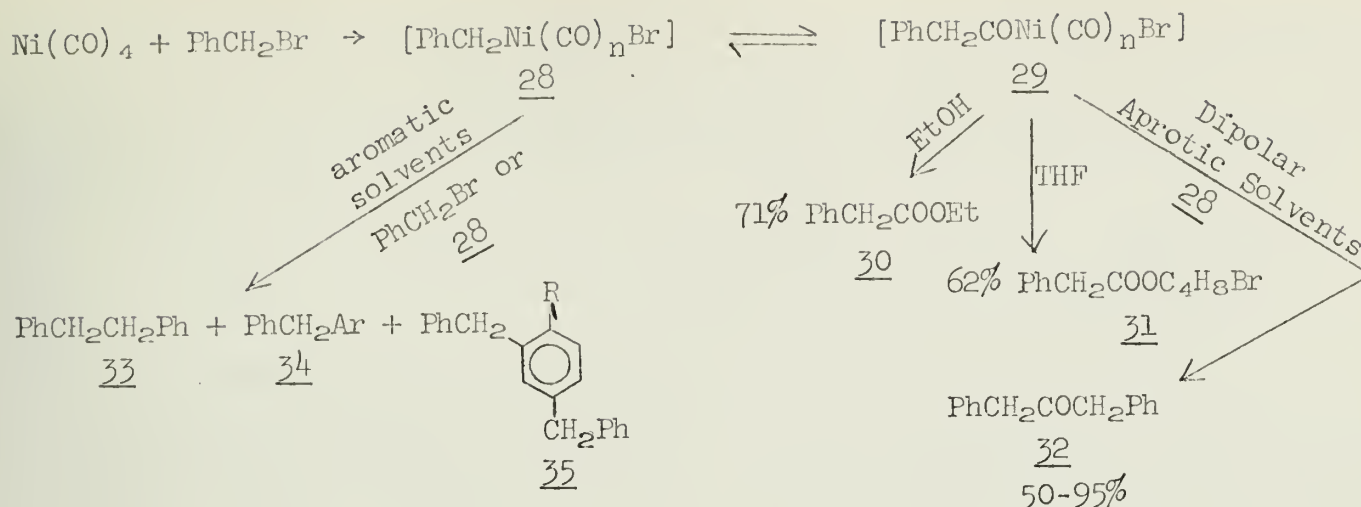


### C. REACTIONS WITH BENZYL HALIDES.

Tsutsumi and Yoshisato<sup>22</sup> studied the reactions of benzyl halides with nickel carbonyl in several solvents, and found a strong solvent dependence on product distribution. Carbon monoxide addition occurred in polar non-aromatic solvents whereas almost no insertion occurred in aromatic solvents (see Figure 3). In the polar non-aromatic solvents, reactivity of the benzyl halides were; I > Br > Cl, whereas in aromatic solvent the activity reversed; Cl > Br > I. The authors report an increase in reaction rate with increasing "polarity" of solvent. A similar effect was observed by Angelici and Leach<sup>23</sup> who found that solvents with donor atoms such as nitrogen and oxygen accelerate the rate of substitution of nickel carbonyl by triphenyl phosphine. In Tsutsumi's reaction scheme the formation of ester 30 could have resulted from alcoholysis of complex 29. The ester 31 was thought to

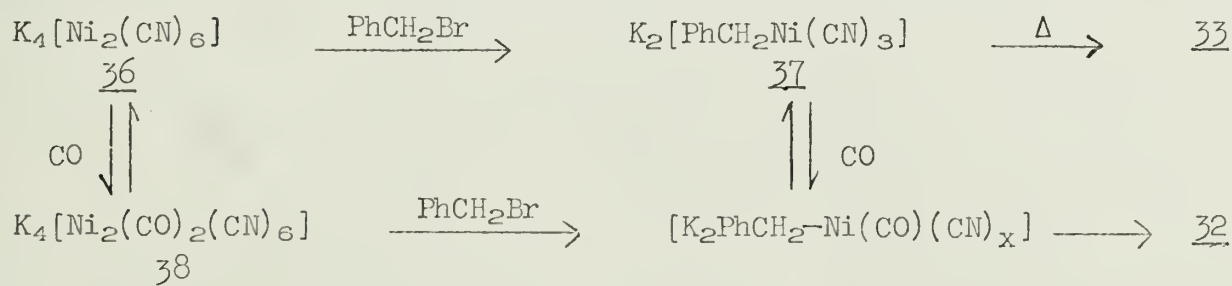


Figure 3



result from ring opening of tetrahydrofuran resulting from attack by 29. Dibenzyl ketone (32) most probably resulted from a reaction between 28 and 29 since reaction of benzyl bromide with 28 or 29 was shown to be unlikely in dipolar aprotic solvents; when two moles of benzyl bromide per mole of nickel carbonyl was used in dipolar aprotic solvents, one mole of halide was recovered. A different reaction appears to have taken place in aromatic solvents, where the hydrocarbons 33, 34, and 35 were formed. Bibenzyl (33) could have occurred via a dimerization of 28 or by reaction of 28 with benzyl bromide. Phenyl aryl methane (34) and the dibenzyl aryl compound 35 result from attack of complex 28 on the aromatic solvent. The product distribution would lead one to believe that benzyla-tion occurred by a Friedel-Crafts mechanism since the yield of benzylated solvent was: toluene, 58%; benzene, 36%; and chlorobenzene, 4%, and in toluene only ortho and para products were formed. However, a control experiment with benzyl bromide and nickel bromide under the same reaction conditions did not yield any Friedel-Crafts reaction products. Angelici and Leach<sup>23</sup> found a related solvent effect in substitution reactions of nickel carbonyl with triphenylphosphine. They reported that benzene derivatives with electron releasing groups accelerate the substitution reaction and state that these results parallel the stabilities of chromium and molybdenum complexes in substituted benzenes where electron releasing groups were found to stabilize the complexes. Also, cyclohexene gave rate acceleration compared to cyclohexane, indicating interaction between the olefinic  $\pi$  system and the nickel atom.

Tsutsumi<sup>24</sup> and co-workers recently studied the reaction of benzyl bromide with potassium hexacyanonickelate (36) in the presence of carbon monoxide and aqueous acetone under a nitrogen atmosphere at temperatures from 0-20°. Compound 36 forms a dark red solution which turns to yellow upon addition of benzyl bromide. The yellow intermediate 37 was stable at 0° for several hours and addition of carbon monoxide gave 34% dibenzyl ketone (32) and 59% bibenzyl (33). When a solution of 37 was raised to 20° C, a "rapid decomposition" was observed, from which 89% 33, 0.6% benzaldehyde, and 2% benzyl alcohol were isolated. When 38 was used as a starting material, reaction with benzyl bromide



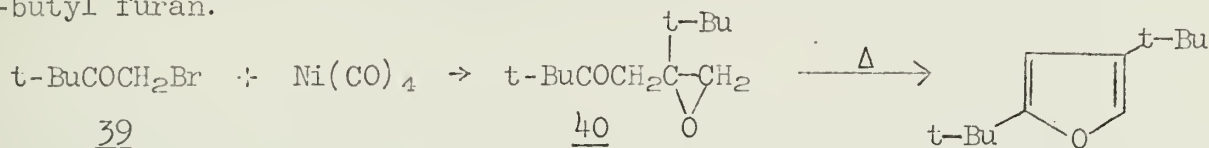
produced 90.4% 32, 3.1% 33, and 0.3% benzaldehyde. Alkyl and aryl halides were found to be much less reactive towards 36 or 38 under the reaction conditions used for benzyl bromide.

#### D. REACTIONS WITH $\alpha$ --BROMO KETONES.

Tsutsumi<sup>25,26</sup> and Yoshisato have reported reactions of  $\alpha$ -bromo ketones with nickel carbonyl that provide new routes to  $\beta$ -epoxy ketones and 2,4-disubstituted furans.

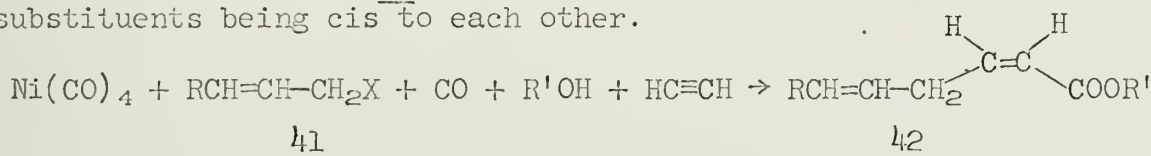


Phenacylbromide reacted with nickel carbonyl in dimethylformamide at room temperature to give 2,4-diphenylfuran. The reaction appears to be solvent or temperature dependent since in tetrahydrofuran at 50° the predominant product was 1,2-dibenzoyl ethane. Bromomethyl-tert-butyl ketone (39) and nickel carbonyl reacted in dimethylformamide at 30° to give the β-epoxy ketone 40 which thermally converted to 2,4-di-tert-butyl furan.

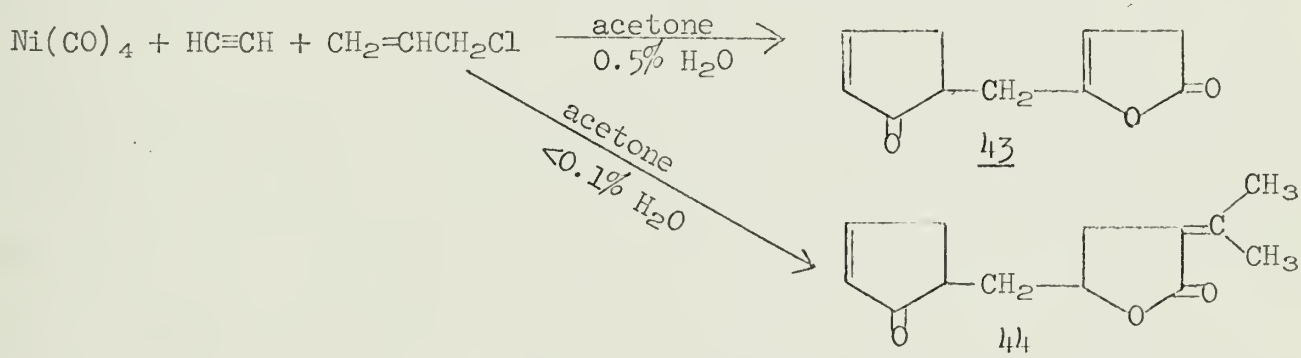


#### E. REACTIONS WITH ALLYL BROMIDES.

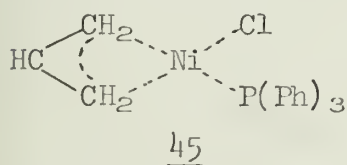
Chiusoli and Cassar<sup>7</sup> have reviewed the nickel catalyzed reactions of allyl halides and present the following observations: 1) Allyl halides (41) react with nickel carbonyl in protic solvents to give β,γ-unsaturated products and in the presence of acetylene give compounds (42) with double bonds in the α,β and δ,ε positions, the α,β substituents being cis to each other.



2) If a compound is a secondary halide that can rearrange to a primary halide, it reacts to give primary allyl derivatives while tertiary halides rearrange to secondary halides. 3) If nickel carbonyl and 41 react in ethers or aromatic hydrocarbons, the products are acyl halides. 4) One of the main side reactions in the carbonylation of allyl halides is dimerization of the allyl group. 5) If nickel carbonyl, acetylene and 41 react in solvents such as ethers, ketones, or esters, acyl halides form, then readily cyclize to lactones. For example, allyl chloride, acetylene, and nickel carbonyl react in acetone containing 0.5% water to form 43. If the water content is below 0.1%, then a secondary reaction with acetone occurs to form 44 as the main product. 6) Isolation of the π-allyl nickel triphenylphosphine chloride complex 45

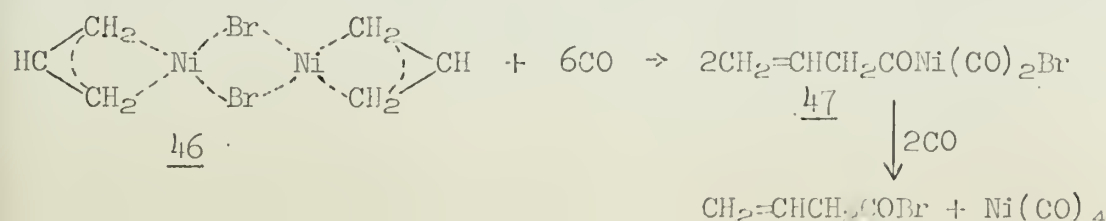


added support to the hypothesis that π-allyl nickel complexes are formed as catalysts in polymerization and carbonylation reaction of allyl halides.



Heck<sup>13</sup> followed the absorption of carbon monoxide into a solution of π-allyl nickel bromide 46 by observing the infra-red spectra of the solution. There was a decrease in the rate of gas absorption after about two-thirds of the carbon monoxide had been absorbed. At this time, an infrared spectrum had a strong band at 4.78 μ and a weak band at 5.72 μ. These absorptions correspond

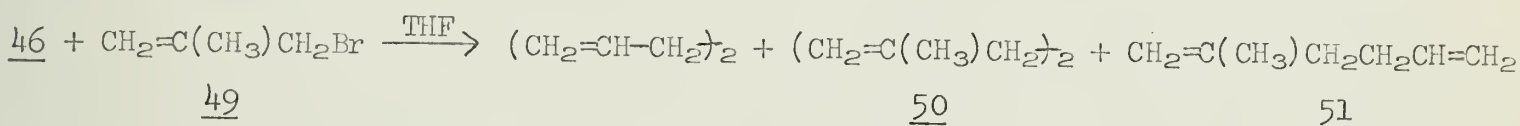
to the expected spectrum of a butenoyl nickel dicarbonyl bromide intermediate 47. After completion of carbon monoxide absorption, only a nickel carbonyl band at 4.9 μ and an acyl bromide band at 5.5 μ were visible. Chiusoli<sup>27</sup> and co-workers studied the





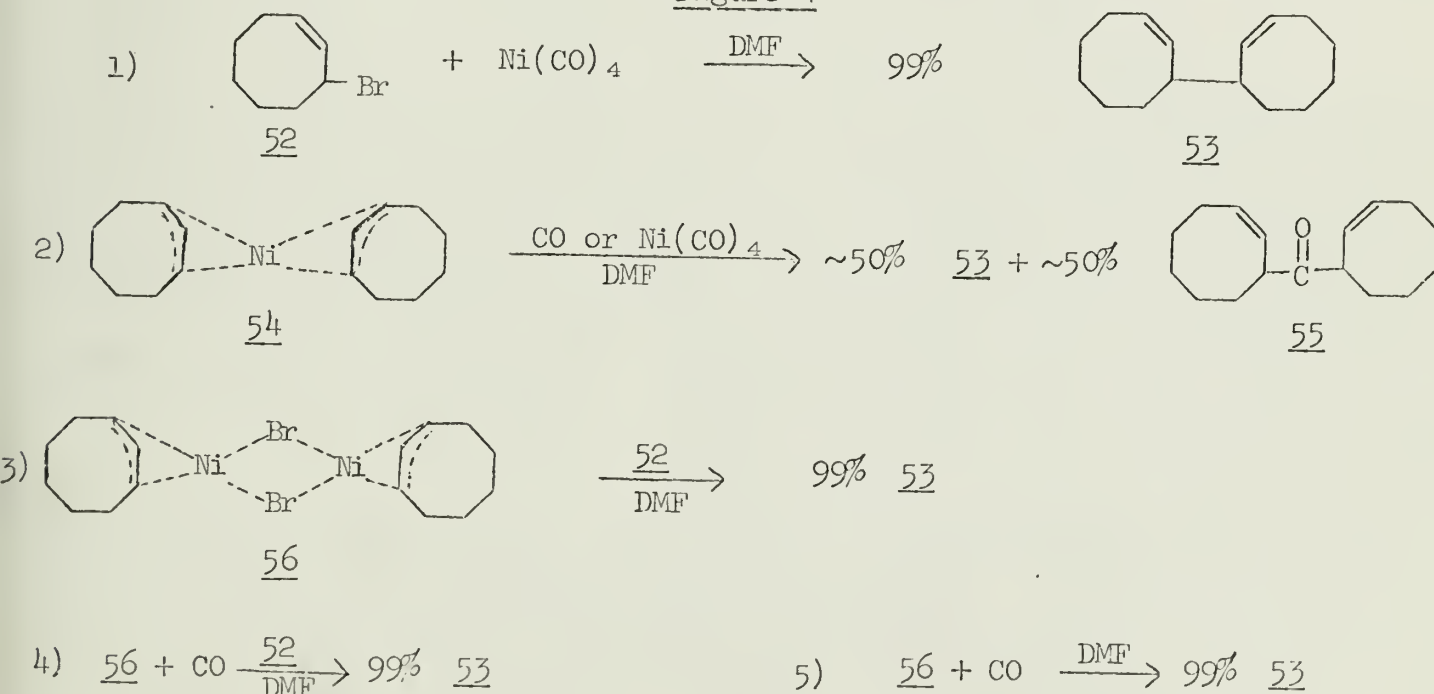
coupling and carbonylation reactions of allyl bromide catalyzed by nickel carbonyl using carbon-14 labeled allyl bromide (48). They obtained 1,5-hexadiene from the coupling reaction and found the radioactivity of both allylic groups equally distributed between the terminal carbon atoms of the former allyl groups. Recovered allyl bromide was also found to be rearranged so that C-1 and C-3 each had 50% of the radioactivity. These workers

concluded from the labeling experiments that allyl bromide was in equilibrium with 46. Corey<sup>28,29</sup> and co-workers observed an equilibrium between 46 and methallylbromide 49. They added 49 to a solution of 46 in tetrahydrofuran and found a mixture of all three possible coupling products, diallyl, bimethallyl (50), and allylmethallyl (51) (glpc). These workers then demonstrated that the reaction of nickel carbonyl and

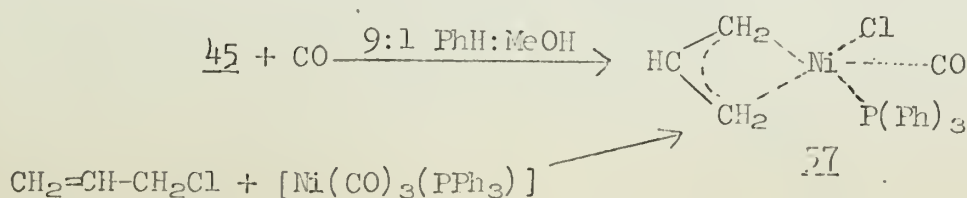


allylic halides is reversible by preparing  $\pi$ -methallylnickel bromide from nickel carbonyl and 49, then forming nickel carbonyl by adding carbon monoxide to a solution of  $\pi$ -methallylnickel bromide. It was noted that the presence of carbon monoxide accelerated the allylic coupling reaction. They further demonstrated yet another equilibrium which exists between  $\pi$ -allylnickel (0) complexes and  $\pi$ -allylnickel (I) complexes, by subliming a yellow nickel (0) complex from a solution of red nickel (I) complex. Discovery of the latter equilibria led to a series of five experiments (Figure 4) which proved that  $\pi$ -allylnickel (I) complexes are the reactive intermediates in the reactions of nickel carbonyl and allyl bromides (such as 2-cyclo-octenyl bromide 52), and that  $\pi$ -allylnickel (0) complexes 54 give different products.

Figure 4

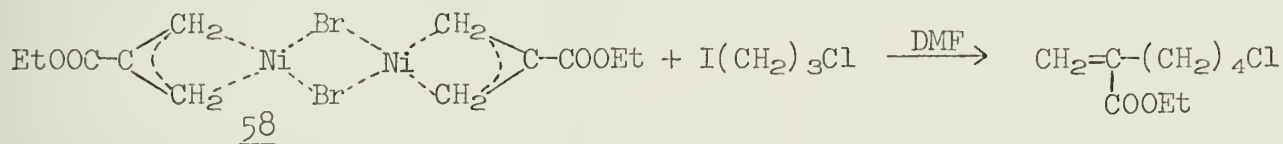


Chiusoli<sup>30,31</sup> and Guerrieri have isolated what they believe are  $\pi$ -allylic penta-coordinated nickel complexes 57 (infrared, nmr, and X-ray analysis). The complexes were prepared by adding carbon monoxide to 45 or by adding allyl chloride to nickel triphenylphosphine tricarbonyl. Postulating pentacoordinated complex with solvent as





a ligand in dipolar aprotic solvents may explain the change in rate levels and change in products observed by several workers.<sup>19,22,23,25,32</sup> Corey<sup>32</sup> and Semmelhack examined the reaction of  $\pi$ -allylnickel complexes such as 58 and found them to be inert towards alkyl halides in hydrocarbons and ethers, but in more polar "coordinating" media such as dimethylformamide, N-methylpyrrolidone or hexamethyl phosphoramide the reaction proceeded well even in the presence of hydroxy and carbonyl functional groups.

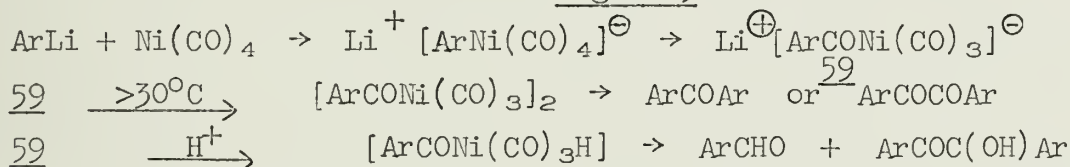


Corey<sup>33-35</sup> has used doubly allylic  $\alpha,\omega$ -dihalides and nickel carbonyl to synthesize cyclic compounds with up to eighteen carbon atoms in the ring.

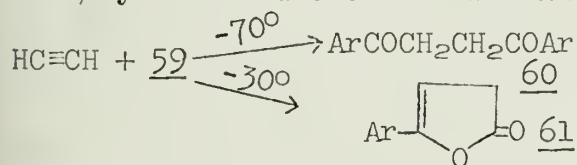
#### IV. CARBONYLATION REACTIONS WITH NICKEL CARBONYL AND ORGANOLITHIUM REAGENTS.

Tsutsumi and Ryang<sup>36</sup> prepared phenyllithium in ether and bubbled carbon monoxide through the solution at  $-70^\circ$  to produce benzophenone in 55% yield. Later, Tsutsumi<sup>37</sup> and co-workers added nickel carbonyl to ether solutions of organolithium compounds at  $-70^\circ$  and in these reactions aryllithiums gave acyloins while alkyl lithiums gave symmetrical ketones. These products could be explained by postulating that the intermediates in these reactions had varying thermal stability and chemical reactivities. The temperature dependence of reactions between aryllithiums and nickel carbonyl was further examined by Tsutsumi<sup>38</sup> and co-workers who found that the formation of ketones and acyloins from aryllithiums and nickel carbonyl could be explained by postulating a lithium aroylnickel carbonyl intermediate(59) as in Figure 5. A salt-like black

Figure 5



product was obtained from reaction of a 1:1 molar ratio of p-tolyllithium:nickel carbonyl. This black product was insoluble in organic solvents, ignited in air, gave toluoin on hydrolysis and para-tolil when it was thermally decomposed at  $110^\circ$  in toluene. The black solid was assumed to be 59. Tsutsumi<sup>39</sup> and co-workers have found that two moles of 59 will react with one mole of acetylene at  $-70^\circ$  in ether to give 1,4-diketones (60) in yields of 47-74%. At  $-30^\circ$   $\gamma$ -lactones (61) were produced in 2-24% yields. These workers examined what they believe to be the specific role of the

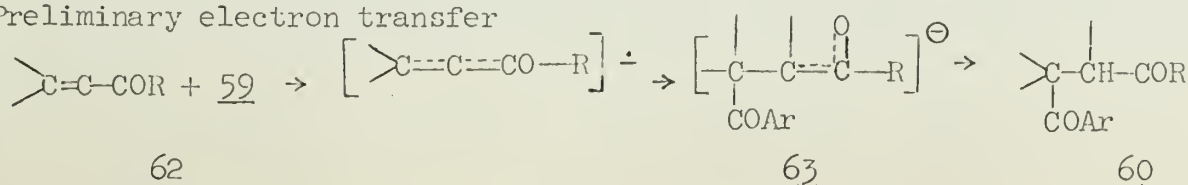


nickel and lithium atoms in the reaction with acetylenes to produce 60. No evidence for insertion of acetylene into a carbon-iron sigma bond or into a complex of aryl Grignard and nickel carbonyl could be obtained. While hydrolysis of

59 gave acyloins, hydrolysis of other acyl- or aroylcarbonylmetalates (Fe, W, Cr, Mo) gave aldehydes. This may indicate that aroyltricarbonyl nickelates are dimeric in solution, while other carbonyl metalates are monomeric. A monomer-dimer equilibrium that is temperature dependent may explain why one sees apparent reaction from dimeric nickelates at  $-70^\circ$ , and from monomers at  $-30^\circ$ . Corey and Hegedus<sup>40</sup> recently reported an alternate method of synthesizing 1,4-dicarbonyl compounds (60) by adding an  $\alpha,\beta$ -unsaturated ketone (62) to a solution of lithium acyl- or aroylnickel carbonylate 59. Three possible mechanisms were presented (see Figure 6), however, no observations were reported as support for any mechanism.

Figure 6

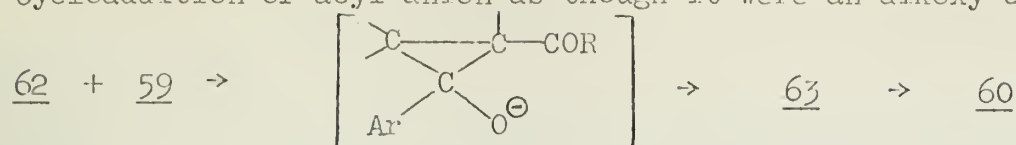
1) Preliminary electron transfer



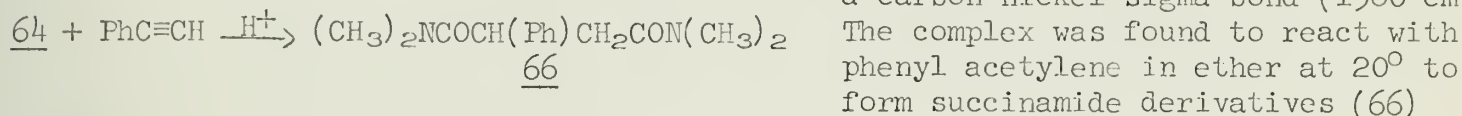
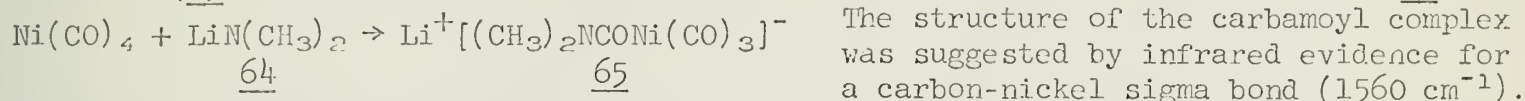


2) Direct acyl anion transfer  $\underline{62} + \underline{59} \rightarrow \underline{63} \rightarrow \underline{60}$

3) Cycloaddition of acyl anion as though it were an alkoxy carbene



Tsutsumi<sup>41</sup> and co-workers observed the formation of lithium carbamoylnickel carbonylate (65) from the reaction of nickel carbonyl and lithium dimethyl amide (64).



The structure of the carbamoyl complex was suggested by infrared evidence for a carbon-nickel sigma bond ( $1560\text{ cm}^{-1}$ ).

The complex was found to react with phenyl acetylene in ether at  $20^\circ$  to form succinamide derivatives (66)

probably by a mechanism analagous to the reactions of acetylenes with acyl nickel carbonylates.

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# RECENT EXAMPLES OF VINYL CATION INTERMEDIATES

Reported by James A. Barron

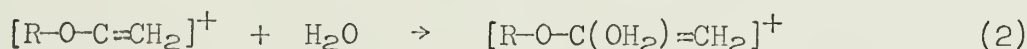
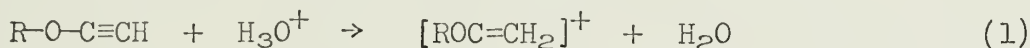
November 6, 1969

For many years, vinyl cations were reputed to be unstable intermediates in organic reactions.<sup>1</sup> The primary reason for this reputation was the unreactivity of vinyl halides under solvolytic conditions. Thus, while alkyl bromides react readily with silver nitrate at room temperature, vinyl bromide remains unchanged by this reagent for several days. Since the first proposal of a vinyl cation intermediate in the alkaline decomposition of nitroso-oxazolidones in 1951,<sup>2</sup> however, there has been an ever increasing interest in these intermediates. It will be the purpose of this seminar to review the most recent and well-documented examples of vinyl cation intermediates, paying particular attention to those studies which focus directly on the question of the stability and reactivity of such intermediates.

## PROTONATION OF ACETYLENE DERIVATIVES

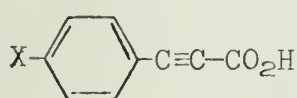
Typical of the early work implicating vinyl cations are the acid catalyzed hydrations of acetylene derivatives. Because much of this work has been previously reviewed,<sup>3,4</sup> only the most recent studies will be discussed in detail here.

In 1944 Jacobs and Searles studied the hydration of acetylenic ethers in acid media.<sup>5</sup> They found such reactions to be first order in the ether and first order in acid. The following mechanism was proposed, in which the authors believed the protonation of the acetylenic ether to be rate limiting (Step 1).



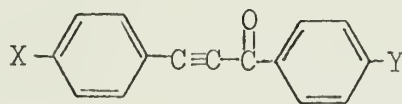
Several years later, Drenth and co-workers undertook an extensive study of the hydrations of acetylenic ethers and thioethers. Their work confirmed that the first step of Jacobs and Searles' mechanism was indeed rate limiting<sup>6,7</sup> and that the addition of water occurred in a step subsequent to the protonation.<sup>8,9</sup> All of their results are consistent with rate limiting formation of a vinyl cation.

More recently, Noyce and co-workers have studied the acid catalyzed hydration of a series of acetylene derivatives; phenylpropionic acid<sup>10</sup> (1), phenylbenzoylacetylene<sup>11</sup> (2), and phenylacetylene<sup>12</sup> (3); proposing rate limiting formation of a vinyl cation in each case.



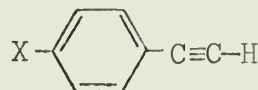
1

- a, X = OCH<sub>3</sub>
- b, X = CH<sub>3</sub>
- c, X = H
- d, X = Cl



2

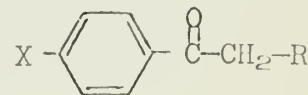
- a, X = H Y = H
- b, X = CH<sub>3</sub> Y = H
- c, X = OCH<sub>3</sub> Y = H
- d, X = H Y = CH<sub>3</sub>
- e, X = H Y = NO<sub>2</sub>



3

- a, X = H
- b, X = OCH<sub>3</sub>
- c, X = CH<sub>3</sub>
- d, X = Cl

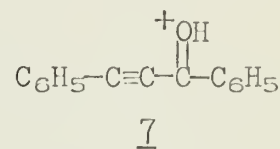
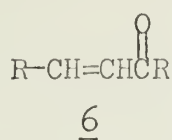
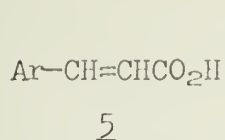
Upon reaction in aqueous sulfuric acid, all compounds showed good pseudo-first order kinetics and gave the corresponding ketone products (4) in essentially quantitative yields.<sup>10,11,12</sup> In addition, the phenylpropionic acids and the phenylacetylenes gave linear plots of log (k) vs. -H<sub>0</sub> with nearly unit slopes.<sup>10,12</sup> The phenylbenzoylacetylenes exhibit a somewhat different behavior. The conversion to the diketone (4b) was relatively slow in 60% sulfuric acid, quite rapid in 80% sulfuric acid, and appeared to exhibit a blend of two different behaviors between the two extremes. Near 60% acid the rate was proportional to the acidity of the medium, while at high acidities (above 75% H<sub>2</sub>SO<sub>4</sub>) it approached a limiting value.



- 4 a, R = CO<sub>2</sub>H
- b, R = COC<sub>6</sub>H<sub>5</sub>Y
- c, R = H



It is interesting to examine this apparently inconsistent behavior of phenylbenzoylacetylene; for while unsaturated acids such as 5 have been shown to hydrate with rate limiting protonation to give a carbonium ion,<sup>13</sup> unsaturated ketones (6) hydrate with rate limiting protonation of a hydroxyenol intermediate.<sup>14</sup> The initial ultraviolet



spectrum of 2 was found to be dependent on the acidity of the medium, an indication that 2 is basic, protonating to form the oxonium ion (7). When the first order rate constants for 2 were corrected for the extent of protonation at a given acidity, plots of  $\log k_{\text{corr}}$  vs.  $-\text{H}_0$  were found to be linear with slope  $0.927 \pm .01$ . It can be seen from Table I that the rates of hydration of the substituted phenylbenzoylacetylenes are most sensitive to changes in the phenyl ring substituents (X), while their basicities are most affected by changes in Y, the benzoylphenyl substituents. The authors reasoned that if 7 were involved in the actual reaction path, the relative rates of hydration in 60% sulfuric acid of 2a and 2b should be in a direct one to one relationship with their basicities. This was not observed. Thus, they concluded that oxonium ion formation was merely a diversionary side reaction and that the hydration proceeded directly from the unprotonated ketone.

With the necessary corrections for compound 2 in mind, the results for all three compounds are analogous. Pseudo-first order kinetics and general acid catalysis were taken to be consistent with two kinds of mechanisms. One involves rate limiting proton transfer to carbon, the other an addition of water to a cationic species present in low concentration. In all three cases, Noyce eliminated as rate limiting the addition of water in favor of a protonation step to give a vinyl cation.

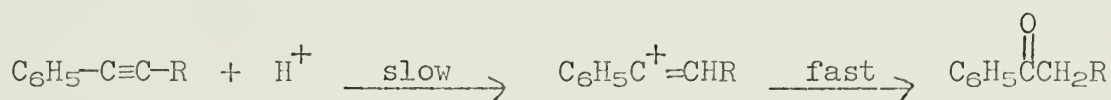


TABLE I. Hydrations of Acetylene Derivatives

Cpd	$-\text{H}_0$	$10^5 k$ ( $\text{sec}^{-1}$ )	$10^5 k_{\text{corr}}$ ( $\text{sec}^{-1}$ )	$k_{\text{H}_2\text{SO}_4}/k_{\text{D}_2\text{SO}_4}$	$\text{pK}_{\text{BH}^+}$	$\rho$
<u>1</u>						-4.77
<u>a</u>	3.38	2840	--	5.30	--	
<u>d</u>	3.38	0.164	--	2.40	--	
<u>2</u>						-4.21
<u>a</u>	4.84	2.42	2.47	2.18 <sup>a</sup>	-6.51	
<u>b</u>	4.83	50.8	52.9	3.02 <sup>a</sup>	-6.18	
<u>c</u>	2.79	55.8	55.8	2.40 <sup>b</sup>	--	
<u>d</u>	5.36	7.39	9.12	--	-6.00	
<u>e</u>	5.36	4.42	4.42	--	-7.77	
<u>3</u>						-3.84
<u>a</u>	1.82	0.0057	--	2.46 <sup>b</sup>	--	
<u>b</u>	0.60	1.91	--	2.70 <sup>b</sup>	--	

a)  $\text{H}_0 = -5.5$       b)  $\text{H}_0 = -2.0$

The evidence for such a mechanism can be summarized as follows: 1) All compounds exhibited normal solvent isotope effects (Table I). Rate limiting addition of water would be expected to show an inverse effect. 2) The spectrophotometrically determined rate constants gave large negative  $\rho$  values when correlated with  $\sigma^+$ . It has been suggested<sup>15</sup> that phenylacetylene data are better correlated by the Yukawa-Tsuno equation. Such large values of  $\rho$  indicate a high degree of positive charge at the benzylic carbon. 3) Secondary deuterium isotope effects have been measured for phenylacetylene.<sup>16</sup> The observed values of  $k_{\text{H}}/k_{\text{D}}$  are 1.11 for 3a and 1.07 for 3b and were obtained by comparing



the rates of 3a and 3b to those of ethynyl-d-benzene and 4-ethynyl-d-anisole respectively. These values have been interpreted in terms of competing  $\alpha$  and  $\beta$  effects. The  $\alpha$  effect arises from hybridizational changes in the transition state. It was calculated from Streitweiser's equations<sup>17</sup> to be 0.77. The  $\beta$  effect is normally explained as arising from hyperconjugative interactions between the isotopically labelled C-H bond and the developing vacant p orbital as in Figure 1. The demand for such interaction has

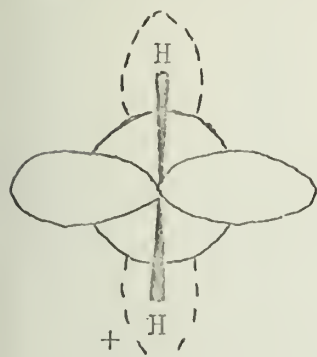


Figure 1.  
Hyperconjugative  
overlap in a vinyl  
cation

has been shown to decrease as the carbonium ion character decreases.<sup>17,18</sup> The values of 1.50 and 1.44 obtained by Noyce are consistent with that observed by Shiner<sup>19</sup> for the solvolysis of cis-4-t-butylcyclohexyl brosylate-trans-2-d, ( $k_H/k_D = 1.44$ ), a reaction in which the isotopic bond and the developing p orbital are also nearly parallel.

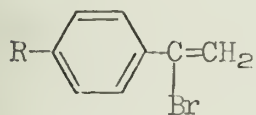
Phenylacetylene was also observed to undergo acid catalyzed exchange of acetylenic hydrogen to the extent of 1.13% after 85 minutes in 40%  $D_2SO_4$ -aqueous ethanol solution.<sup>12</sup> Although the extent to which this exchange occurs curtails the rate limiting nature of the vinyl cation formation, it does indicate that the vinyl cation is capable of either collapse with solvent to form product or loss of a proton to regenerate starting material.

Finally, it is of value to note that phenylpropionic acid is hydrated 19 times faster than cis-cinnamic acid and that phenylacetylene is hydrated 2.3 times faster than styrene under similar conditions.<sup>20</sup> As vinyl cations are thus seen to be more readily accessible under moderately acidic conditions than their alkyl counterparts, their reputed instability is seriously questioned.

#### DIRECT SOLVOLYSIS REACTIONS

Prior to 1968 there was only one reported example of a vinyl cation intermediate generated by the direct heterolytic cleavage of the bond between a vinyl carbon and a leaving group.<sup>21</sup> This lack of solvolytic studies can probably be attributed to the known inertness of vinyl halides to solvolytic conditions. However, as Peterson<sup>22</sup> and Miller<sup>23</sup> have noted, the literature previous to the current decade is lacking in a definitive study of the reactions of vinyl halides with silver nitrate. In fact, the "known inertness" mentioned above was based almost entirely on data for simple unsubstituted vinyl halides where no stabilization of a developing positive charge could occur. As will be discussed, vinyl halides, as well as other vinyl derivatives, are indeed slow to solvolyze when compared to their alkyl counterparts, but by no means inert. Their solvolytic lethargy is, as suggested in the acetylenic protonation studies, not so much a result of the instability of the cationic intermediate, but likely due to ground state stabilization.

The first report of a vinyl cation from solvolysis came in 1964 from Grob and Cseh in a study of  $\alpha$ -bromostyrenes (8).<sup>21</sup> The evidence for vinyl cation formation via  $S_N1$  solvolysis is condensed as follows. 1) The reactions are first order. The determined rate constants appear in Table II. 2) The nitro compound (8e) exhibited only second-order kinetics and was unreactive in the absence of base below 190°. 3) Preparative solvolyses gave only the corresponding acetophenones with the exception of that of  $\alpha$ -bromostyrene which also gave 22% of phenylacetylene. 4) The various substituted phenylacetylenes were found to be stable to the reaction conditions. 5)  $\alpha$ -Bromostyrene reacted ten times faster in 50% ethanol than in the less ionizing 80% ethanol. 6) Compound 8b reacted with silver nitrate after slight warming in 80% ethanol to give silver bromide. The nitro compound gave no precipitate after several days.



- 8  
a, R = NH<sub>2</sub>  
b, R = OCH<sub>3</sub>  
c, R = NHCH<sub>3</sub>  
d, R = H  
e, R = NO<sub>2</sub>

The authors therefore claimed that the reactions of compounds 8a, b, c, and d proceeded via an  $S_N1$  type mechanism to form a vinyl cation and that the nitro compound proceeded solely by an E2 elimination pathway. It seems unlikely,<sup>23</sup> however, that the



workers could have observed enough variation of the rate on the addition of excess triethylamine to detect a competitive E2 elimination pathway in the formation of

TABLE II

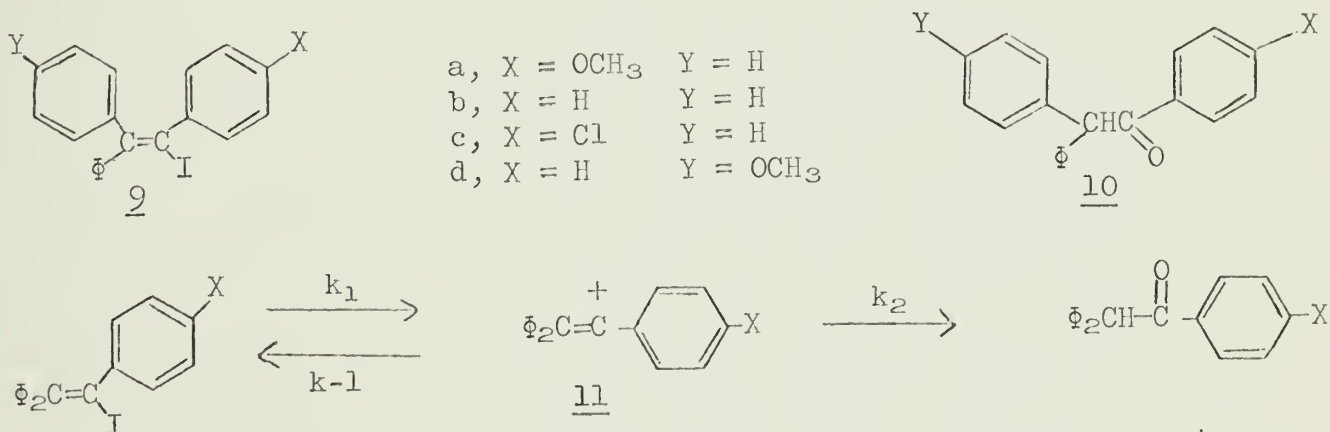
Cpd.	Temperature	$10^5 k$ (sec $^{-1}$ ) *	$k_{rel}^{100}$
$\delta_a$	0.00	9.57 (9.49) **	$5.5 \times 10^8$
$\delta_b$	100.10	3.60 (3.60)	$8.5 \times 10^3$
$\delta_c$	115.20	3.80 (3.92)	$2.2 \times 10^3$
$\delta_d$	170.00	6.00 (6.80)	1

\*In 80% ethanol and 1 molar equivalent of triethylamine.

\*\*Values in parentheses are in the presence of 0.05 M triethylamine.

phenylacetylene from  $\alpha$ -bromostyrene. Although an E2 process can probably not be completely ruled out, analogy to Noyce's exchange experiments with phenylacetylene suggests that a benzylic vinyl cation is capable of deprotonation to give phenylacetylene. Grob's rate data do not correlate well with  $\sigma^+$  constants. A curve is obtained with  $\rho < -4.5$ . Thus the observed rate accelerations do not parallel the known electrical properties of the substituents.

Miller and Kaufman have recently undertaken studies aimed at clarifying the mechanism of vinyl halide solvolysis. These workers have investigated the solvolysis of several triaryliodoethylenes (9) in aqueous dimethylformamide.<sup>23</sup> They report that all compounds except 9a exhibited first-order kinetics for several half lives. The rate of reaction of 9a was found to decrease with time. The products of the reactions were the corresponding ketones (10). The authors formulated a mechanism in which a vinyl cation is formed. Additional observations were made concerning this mechanism. 1) Added nucleophiles did not increase the rates, but these rates were sensitive to changes in



the  $\alpha$ -phenyl substituent (X). A three point plot of  $\log (k/k_0)$  vs. the  $\sigma^+$  constants of Brown and Okamoto<sup>24</sup> gave  $\rho = -3.6$ . (A better correlation is obtained with the very recent values given by Swain and Lipton,<sup>25</sup>  $\rho = -4.4$ .) This may be compared to values of -3.8 and -4.8 for the hydrations of phenylacetylene and phenylpropionic acid respectively, reactions which have also been postulated to proceed via phenyl stabilized vinyl cations. 2) Compound 9a gave definitely curved first-order rate plots, the rate decreasing during the reaction. Added iodide (0.01 M) depressed the rate by 40% and tended to make the plots linear. The authors interpreted these results in terms of common ion rate depression. They also argued that the reversible formation of a free vinyl cation which could discriminate against water in favor of low concentrations of iodide was thus implicated. Such discrimination can be evaluated from the kinetic equation (eq. 5) relating the observed rate constant to the rate constants for ionization ( $k_1$ ), internal return ( $k_{-1}$ ), and product formation ( $k_2$ ) in terms of  $k_{-1}/k_2$ . For 9a at 130.5°,  $k_{-1}/k_2$  was reported to be approximately 40. Similar large values have been suggested for stable carbonium ions.<sup>26</sup> Rate depression was also observed for 1-anisyl-2,2-diphenylbromoethylene,  $k_{-1}/k_2 \approx 10$ . The unsubstituted compound (9b) did not show rate depression, however. It was suggested therefore that selectivity is not a property of all vinyl cations, but in this case arises from the increased stability



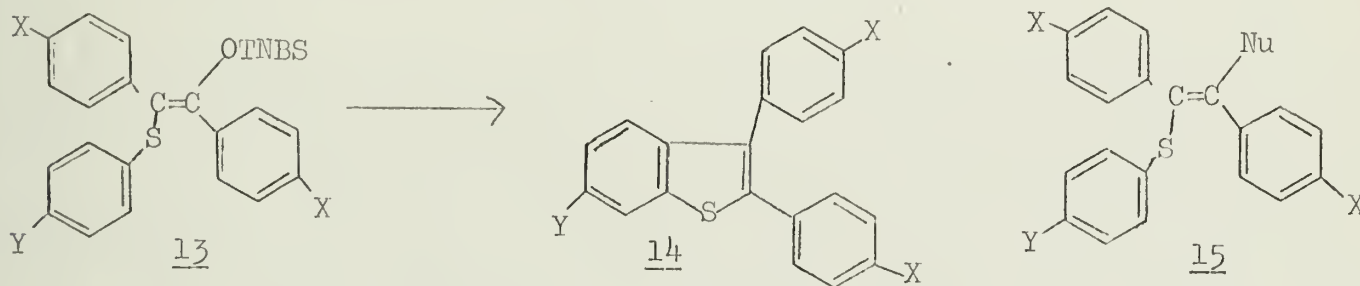
$$k_{\text{obs}} = k_1 / \{1 + (k_{-1}/k_2) [I^-]\} \quad (5)$$

substituent (Y) was noted and interpreted to mean that very little delocalization of positive charge onto the  $\beta$ -carbon occurs as in 12. This is also predicted by theoretical calculations.<sup>27,28</sup>



Miller's results indicate that vinyl cations are accessible from solvolysis and that these ions appear to behave in a manner similar to their alkyl counterparts.

Modena and co-workers<sup>29</sup> have recently observed common ion rate depression and normal salt effects while postulating vinyl cations in the solvolysis of 1,2-diaryl-2-aryl-mercaptovinyl 2,4,6-trinitrobenzenesulfonates (13). The products were found to be benzo-(b)thiophene derivatives (14) when the reactions were run in inert solvents or substitution products (15) when weak nucleophiles were present.



With acetone as solvent, the reactions were first-order up to 90% completion at 25°. Rate depression was observed to the extent of 20% on addition of 0.082 M lithium trinitrobenzenesulfonate (LiTNBS). This effect was confirmed with experiments using <sup>35</sup>S labelled LiTNBS. Modena<sup>29b</sup> found 19.5% incorporation of labelled TNBS into recovered starting material after 45% reaction.

The rates were found to be quite sensitive to changes in the X substituent,<sup>29b</sup> k being larger for the 4,4'-dimethyl compound than the 4,4'-dichloro compound. Correlation with  $\sigma^+$  constants is complicated, however, because the authors apparently were unable to obtain the mono-substituted compounds. The mercaptoaryl substituents (Y) were correlated with  $\sigma$  values,  $\rho = -1.5$ . It was suggested that this effect could be explained either in terms of inductive-conjugative stabilization of the carbonium ion through the sulfur atom or anchimeric assistance by sulfur to form a thiocyclopropenium ion intermediate. The extent of possible sulfur participation is currently under investigation by Modena's group.

Rappoport and Cal<sup>30</sup> have suggested the intermediacy of vinyl cations in the solvolysis of trianisylvinyl halides. The reactions of the chloride and bromide compounds in aqueous ethanol at 120° are first-order. The rates are not affected by added acetate or p-toluenethiolate, but the observed products are nucleophile dependent. Ketones and ethers are produced in aqueous ethanol, while esters and thioethers predominate in the presence of the above-mentioned nucleophiles. Common ion rate depression was judged to be unimportant for the bromide.

TABLE III

Cpd.	k (sec <sup>-1</sup> )*	k <sub>rel</sub>
<u>16a</u>	0.699**	13,500
<u>16b</u>	2.16	41,700
<u>16c</u>	5.18 x 10 <sup>-5</sup>	1

\*Acetolysis rate constant at 150.8°.

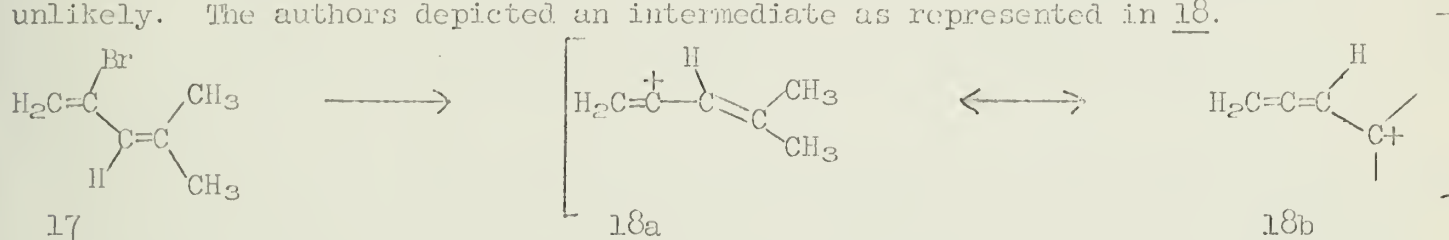
\*\*Extrapolated from lower temperatures.

reaction showed no solvent isotope effect, and a dramatic rate increase was observed in going from the tosylate to the trifluoromethanesulfonate (Table III).

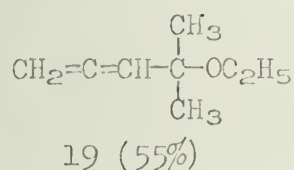
Although Rappoport and Cal found triphenylvinyl halides inert to their solvolytic conditions, Jones and Mannes<sup>31</sup> have recently reported evidence for the formation of a triphenylvinyl cationic intermediate from solvolysis. These workers have investigated the acetolysis of some triphenylvinyl sulfonates. The fluorosulfonate (16a), the trifluoromethanesulfonate (triflate, 16b), and the tosylate (16c) exhibit first-order kinetics and form the triphenylvinyl acetate as the major product. The authors ruled out an addition-elimination mechanism or an S<sub>N</sub>2 displacement on the basis of the following evidence. Changes in the initial sodium acetate concentration showed only minor effects on the rates, the isotope effect, and a dramatic rate increase was observed in



It should be mentioned that all the cationic intermediates discussed thus far are capable of extensive stabilization by an  $\alpha$ -aryl group. Grob has investigated the ability of an adjacent double bond to similarly stabilize a vinyl cation intermediate.<sup>32</sup> Some substituted butadiene compounds were allowed to undergo solvolysis at 100° in 80% ethanol. The results of 2-bromo-4-methyl-1,3-pentadiene (17) are typical. The reaction was found to be first-order, the rate was insensitive to the addition of four molar equivalents of triethylamine, and the reaction was approximately 20 times faster in the more ionizing 50% ethanol. An addition-elimination mechanism was therefore considered unlikely. The authors depicted an intermediate as represented in 18.

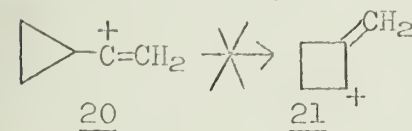


The importance of contributions from 18b is emphasized by the fact that 2-bromo-3-methyl-1,3-pentadiene, a compound lacking the C-4 gem dimethyl groups, reacts only very slowly at 110°. Such contributions are further suggested by product studies for the solvolysis of 17. The predominant product was the ethyl ether (19) in 55% yield. Thus, while a cationic intermediate is strongly implicated, the degree to which this intermediate, and those stabilized by an  $\alpha$ -aryl group, actually represent a formal vinyl cation is perhaps questionable.



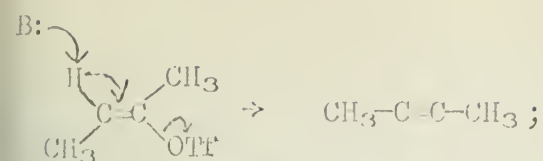
Recently Bergman and Sherrod<sup>33</sup> in California and Hanack and Bässler<sup>34</sup> in Germany presented evidence for vinyl cations stabilized by an adjacent cyclopropyl ring. Bergman studied the reaction of 1-cyclopropyl-1-iodoethylene in aqueous methanol at 150° and in aqueous ethanolic silver nitrate at room temperature. Hanack investigated the behavior of the corresponding chloride compound with silver perchlorate in unbuffered acetic acid at 25° and in aqueous methanol at 150°. The results of these independent studies are in complete accord. Both compounds were found to react immediately with silver ion to form silver halides and cyclopropylmethyl ketone in good yields (90% for the iodide,<sup>33</sup> 80% for the chloride,<sup>34</sup> with 15% cyclopropylacetylene). Bergman reported the formation of ester products in the presence of silver acetate or p-toluenesulfonate. Both groups found first-order kinetics when the solvolyses were carried out at 150° in the absence of silver ion. In addition, the rates were not affected by increasing the concentration of triethylamine up to a three-fold excess. The authors felt that the evidence was best explained by heterolytic cleavage of the carbon-halide bond to form a vinyl cation (20).

The fact that the 2-halo-3-methyl-1-butenes were completely unreactive to silver ion at room temperature indicated electron release from the cyclopropyl ring to be important in the transition state. But, because 20 showed little tendency to rearrange to a cyclobutyl cationic intermediate (21), the authors felt that 20 must retain a high degree of positive charge at the vinyl carbon.

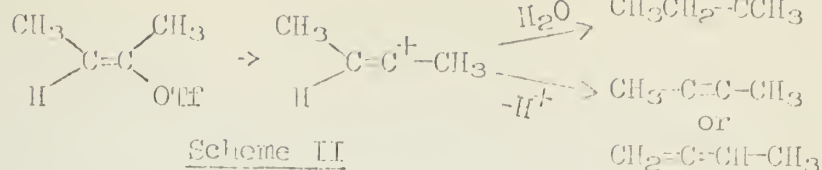


As seen previously, trifluoromethanesulfonate (triflate) is an excellent leaving group.<sup>31,35</sup> Very recently Stang and Summerville<sup>35</sup> have reported the solvolysis of *cis*- and *trans*-2-buten-2-yl triflates in 80% ethanol at 76°. The *trans* compound gave only dimethylacetylene. The *cis* compound gave 33% 2-butanone, 58% dimethylacetylene, and 9% methylallene. The product ratios from the *cis* isomer did not change in the presence of added base, and the products were shown to be stable to the reaction conditions [methylallene did undergo some (5-10%) isomerization to the acetylene]. The authors proposed a mechanism which is a balance between a concerted E2 elimination (Scheme I) and a unimolecular ionization involving a vinyl cation (Scheme II). The olefinic products could arise from either of these mechanisms, but it was suggested that the ketone could occur only *via* solvent capture of a vinyl cation. The reaction rate of isopropenyl triflate was increased 37-fold in the presence of sodium hydroxide. The *trans*-2-buten-2-yl isomer





Scheme I



Scheme II

reacted 40 times more rapidly than the cis isomer. Both of these observations suggest that concerted elimination takes place when the favorable trans geometry is available. The geometrically unfavorable cis isomer reacts via unimolecular ionization to a vinyl cation. This hypothesis is supported by labelling studies. The deuterio trans and deuterio cis compounds were prepared, and  $k_H/k_D$  ratios were found to be 2.09 and 1.20 respectively. While somewhat small, the former is consistent with a primary bond breaking effect, and the latter compares favorably with the magnitude of the  $\beta$  effect discussed in Noyce's phenylacetylene work.<sup>16</sup> These results are confirmed in a similar study by Peterson.<sup>37,38</sup>

Peterson has drawn some interesting comparisons from his vinyl cation work. Based on data for cis-2-buten-2-yl tosylate and 2-butyl tosylate, the relative rate of carbonium ion formation by solvolysis from  $sp^3$  hybridized carbon, compared to  $sp^2$  hybridized carbon, is seen to be  $1.5 \times 10^6$ . As previously discussed studies suggest that vinyl cations may be of comparable stability to alkyl cations (theoretical calculations place the parent vinyl cation between methyl and ethyl cations energetically<sup>39</sup>), this effect is not satisfactorily explained in terms of the instability of the intermediate in the vinyl case. Explanation in terms of ground state stabilization seems more reasonable. Increased  $\pi$  character of the vinyl carbon-leaving group bond and stronger  $\sigma$  bonding due to hybridization differences are the reasons usually given for the stabilization of the vinyl ground state.<sup>23,30</sup>

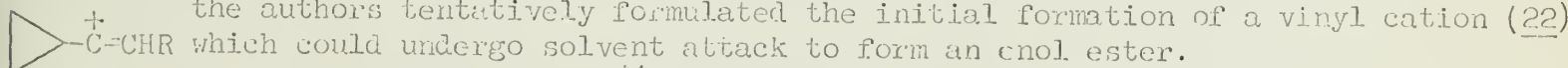
The ratio of rates for 1-phenyl-1-ethenyl tosylate and cis-2-buten-2-yl tosylate is 255, while the corresponding saturated compounds show a rate difference of 5000. Peterson suggests therefore that a phenyl ring is less able to stabilize a vinyl cation than an alkyl one. This may be a consequence of loss of ground state conjugation between the phenyl group and the double bond on going to the transition state leading to a vinyl cation.

A strong preference for a linear over a bent vinyl cation is demonstrated in the ratio of rates ( $>270$ ) for cis-2-buten-2-yl brosylate and cyclohexenyl brosylate. Such a preference is predicted from theoretical calculations.<sup>23,40</sup> Bergman<sup>41</sup> has very recently found stereochemical evidence for the linearity of vinyl cations. Upon treatment of cis- and trans-1-iodo-1-cyclopropylpropenes with silver acetate and acetic acid, each of those isomers gave almost exactly the same mixture of products. As such reactions have previously been shown to proceed via vinyl cations,<sup>33</sup> this evidence was taken to mean that such vinyl cation intermediates are either linear or rapidly equilibrating.

#### MULTIPLE BOND PARTICIPATION

Solvolysis reactions which involve participation of a bond remote to the solvolytic center have received a great deal of attention in the recent literature. Typical of the evidence cited for such participation is the observation of accelerated rates and the formation of rearranged products. If the participating bond is an allenic or triple bond, one can easily envision the formation of vinyl cation intermediates.

Hanack and Haffner have investigated the solvolysis of some 3,4-pentadienyl derivatives.<sup>42</sup> Their product mixtures usually contained substantial amounts of alkylcyclopropyl ketones in addition to some unrearranged material. On the basis of the observed products, the authors tentatively formulated the initial formation of a vinyl cation (22)



22  
 Jacobs and Macomber<sup>44</sup> have recently studied the effects of methyl substitution on the solvolysis of 3,4-pentadienyl tosylates and brosylates under a uniform set of conditions. With the exception of the 1,1-dimethyl substituted derivative, all compounds gave rearranged products, homoallenic participation being kinetically inferred. The effects of methyl substitution on the parent compound can be compactly represented in Figure 2, where the given numbers represent the observed acceleration for the indicated substitution. Jacobs and Macomber preferred to depict a nonclassical



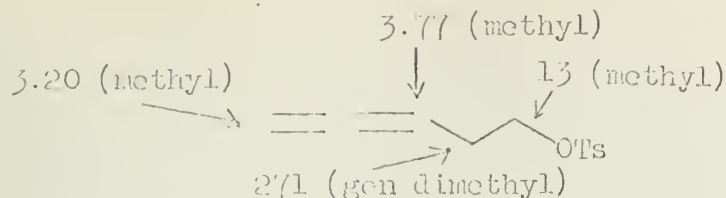
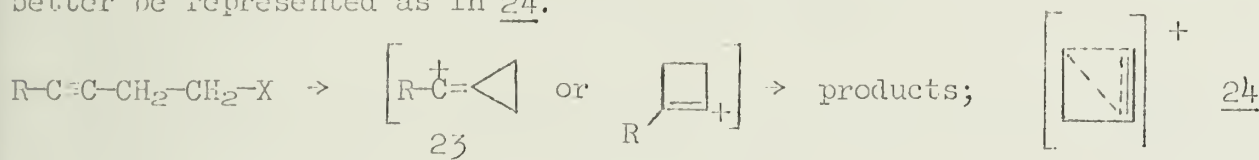


Figure 2

bicyclobutonium type intermediate as being first formed. Bly and Kooch<sup>45</sup> have also studied the effects of methyl substitution in a similar series of compounds. These authors chose to interpret their results in terms of the initial formation of a vinyl cation similar to 22. Both Bly and Jacobs admit that the others' description cannot be excluded on the basis of current evidence. Thus the decision between a classical vinyl cation and a nonclassical bicyclobutonium ion seems to be a matter of preference.

Hanack's group<sup>46</sup> has also undertaken studies of triple bond participation in substituted butyne systems. They found that pentyn-3-yl tosylates, *p*-nitrobenzenesulfonates, and 2,4-dinitrobenzenesulfonates gave predominately cyclobutyl products on trifluoroacetolysis. A mechanism involving the initial formation of an unsaturated cationic species was proposed to account for the observed products. Deuterium labelling studies suggested that the methylenecyclopropyl cation (23) is formed first, subsequently rearranging to give the cyclobutyl products. In a later communication,<sup>47</sup> Hanack reported theoretical calculations which suggested that the initial intermediate might better be represented as in 24.



Peterson and Kamat reported in a preliminary communication that the trifluoroacetolysis of 6-heptyn-2-yl tosylate involved the formation of a transition state resembling a vinyl cation.<sup>48</sup> Subsequent work on this system, however, suggests that this is not the case.<sup>49</sup> The workers prepared 6-heptyn-2-yl tosylate and 6-octyn-2-yl tosylate and subjected them to trifluoroacetolysis. Although five and six membered cyclic products were observed, geometrical considerations of possible vinyl cation intermediates lead Peterson to conclude that they were not resembled in the transition state.

For recent examples of similar reactions which have been suggested to involve vinyl cations, see references 43, 49, and 50.

#### MISCELLANEOUS REACTIONS; PRIMARY VINYL CATIONS

The literature contains several examples of reactions in which primary vinyl cations are suggested as intermediates. Space does not permit their treatment in this abstract. The interested reader should see references 2, 3, 51, 52, and 53 for leading references to many of these reactions.

#### CONCLUSIONS

It is evident that vinyl cations have become acceptable intermediates in organic reactions. The instances of their occurrence encompasses an increasingly wider range of reactions. The evidence in favor of vinyl cations appears to be most substantial in those reactions involving the protonation of acetylene derivatives and the direct heterolytic cleavage of a bond between a vinyl carbon and a leaving group. There is indication that vinyl cations may be of stability comparable to some of their alkyl counterparts.

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# THE DUALITY OF MECHANISM FOR NITRATION IN ACETIC ANHYDRIDE

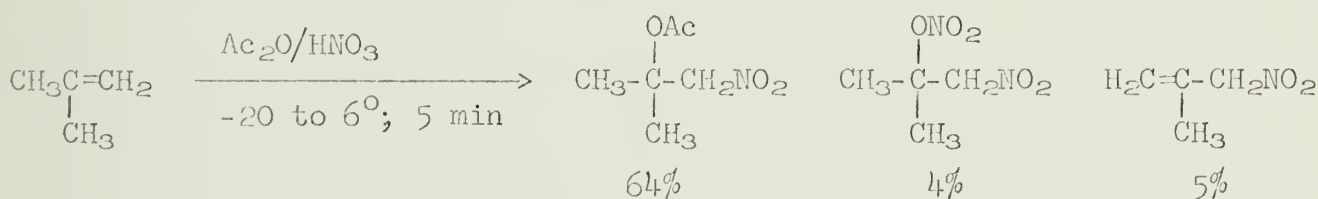
Reported by Alan Brannfman

November 10, 1969

Acetic anhydride is widely used as a solvent for the nitration of compounds susceptible to oxidation or hydrolytic attack by aqueous mixed acid. While the mechanism of aromatic nitration for aqueous mixed acid and for nitric acid solutions in a number of other inert solvents is reasonably well established,<sup>1,2</sup> there remains some uncertainty in the case of acetic anhydride. The anomalously high *o/p* ratios obtained in the nitration of such substrates as anisole and acetanilide by nitric acid in acetic anhydride or,<sup>3-6</sup> more generally by acyl nitrates in organic solvents, provides another apparent reason why nitration under these conditions should be considered separately. Although the nitration of alkenes with nitric acid has been used for many years,<sup>7</sup> the complexity of the mixture of products formed,<sup>7</sup> has discouraged synthetic use of the reaction, and derivatives of nitric acid, particularly  $N_2O_4$ ,<sup>8</sup> and  $N_2O_5$ ,<sup>9</sup> have proved to be of much greater preparative value.

Experimental evidence has been interpreted in the literature to suggest that either protonated acetyl nitrate,<sup>10-13</sup> or nitronium ion,<sup>14-16</sup> or dinitrogen pentoxide,<sup>17,18</sup> may be the effective nitrating agent in acetic anhydride. Recent experimental data have shed new light on the mechanism for the nitration of aromatic compounds in this medium.<sup>19-21</sup> This seminar will attempt to examine the reasoning behind each of the above claims and to determine whether the new information helps to clarify the situation.

Bordwell has treated a series of olefins with 70% nitric acid in acetic anhydride and found the principal product to be generally the  $\beta$ -nitro acetate supposedly formed by Markownikoff addition of  $AcO-NO_2$  to  $C=C$ .<sup>13</sup> Smaller amounts of  $\beta$ -nitroalkenes (unconjugated isomer) are usually also obtained together with small amounts of  $\beta$ -nitro nitrates. The reaction with 2-methylpropene will serve as an illustration. The over-



all yields with alkenes of the type  $RCH_2CH=CH_2$  or  $R_2CHCH=CH_2$  are low and  $\beta$ -nitro nitrates are formed in amounts about equal to those of the  $\beta$ -nitro acetates. The reaction rate is markedly increased by addition of sulfuric acid, while the presence of urea, nitrate ion, or acetate ion, decreases the rate of reaction and increases the proportion of  $\beta$ -nitro nitrate.

Marcus and Fresco have studied the presence of nitronium ions in nitric acid-acetic anhydride mixtures by infrared spectral measurements as shown in Table I.<sup>22</sup>

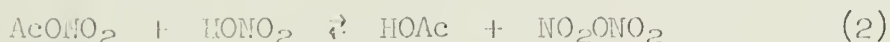
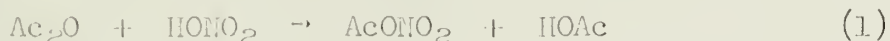
Table I

$Ac_2O$ (Mole %) <sup>a</sup>	Absorbance <sup>b</sup>
0	0.056
8	0.252
18	0.152
31	0.00
47	0.01
81	0.00

<sup>a</sup>The  $HNO_3$  was 99.1% pure. <sup>b</sup> $NO_2^+$  band assigned at  $2360\text{ cm}^{-1}$ .



Their results indicate that the formation of nitronium ions from absolute nitric acid is promoted by low concentrations of acetic anhydride. Vandoni and Viola concluded from vapor pressure measurements of acetic anhydride and absolute nitric acid at  $-10^{\circ}$  that at one-half mole fraction of each component only acetyl nitrate and acetic acid are present.<sup>23</sup> At higher nitric acid concentrations the vapor pressure rises rapidly due to the formation of dinitrogen pentoxide.<sup>23</sup> Similarly, it was concluded from Raman spectral measurements that when excess acetic anhydride is present



the only nitrating agent detectable is acetyl nitrate.<sup>24</sup> With slight excess of nitric acid, dinitrogen pentoxide is observed to be present.<sup>24</sup> Bordwell's experiments were carried out with 70% nitric acid and excess acetic anhydride (after reaction with the water present in the nitric acid, the mole ratio of  $\text{Ac}_2\text{O}$  to  $\text{HNO}_3$  was about 5.5 to 1).

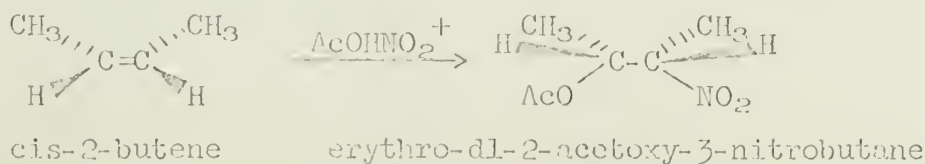
Nitrations run at various temperatures on olefins and anisole were interpreted to mean that addition of 70% nitric acid to acetic anhydride at  $-10^{\circ}$  produces little or no acetyl nitrate.<sup>13</sup> At  $20-25^{\circ}$  addition of nitric acid to acetic anhydride is accompanied by hydrolysis of the acetic anhydride and reaction of nitric acid with acetic anhydride to produce acetyl nitrate. The discovery that nitric acid could be recovered almost quantitatively from the nitration mixture prepared at  $-10^{\circ}$  by precipitation as urea nitrate could be taken to support this view.<sup>13</sup> Addition of urea to a nitrating mixture prepared at  $20-25^{\circ}$  precipitated only 30-35% of the original nitric acid, suggesting that under these conditions 65-70% of the nitric acid has been converted to acetyl nitrate. After one hour the amount of nitric acid remaining was 22%, as judged by urea nitrate precipitation.

The assumption that protonated acetyl nitrate is the reactive species is consistent with the observation by Paul<sup>14</sup> that the rate of nitration of benzene in acetic anhydride is second order in nitric acid (eqn. 4) and that the reaction becomes first order in nitric acid when sulfuric acid is present (eqn. 5). Addition of  $4.45 \times 10^{-5} \text{ M}$  sulfuric acid to  $0.319 \text{ M}$  *o*-xylene in  $3.91 \times 10^{-2} \text{ M}$  nitric acid in acetic anhydride increases the rate by a factor of 19.<sup>12</sup> Bordwell concluded from



this that the effective nitrating species for alkenes and anisole, when the nitrating agent is prepared at  $15-25^{\circ}$  and the reaction is run for less than five minutes at  $-20^{\circ}$  to  $+20^{\circ}$ , is protonated acetyl nitrate. Nitrations allowed to continue beyond five minutes often developed a deep blue color-characteristic of nitroso compounds. Also the yields were not improved by extending the reaction time. Sulfuric acid increases the concentration of protonated acetyl nitrate and thereby promotes the reaction.

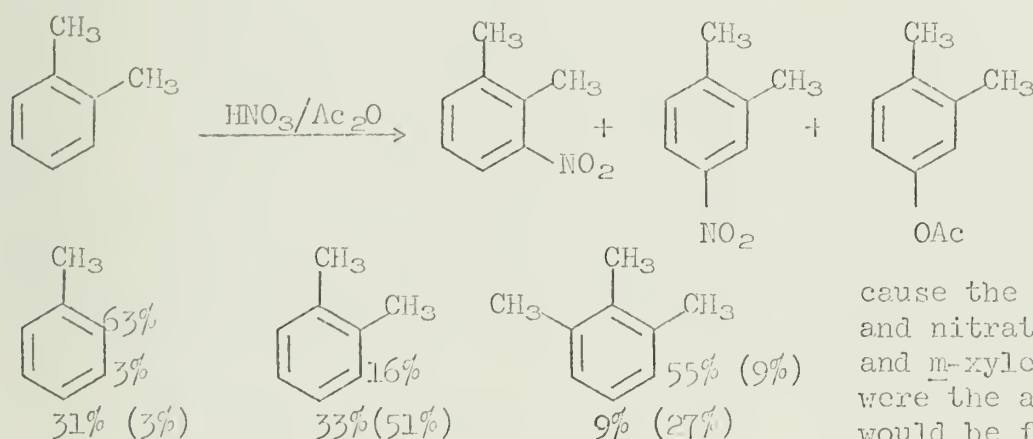
The dissociation of protonated acetyl nitrate to acetic acid and nitronium ion, does not appear to be appreciable in the medium used, since the nitration of *trans*-2-butene gives 65% *threo-dl*-2-acetoxy-3-nitrobutane (*cis* addition), and *cis* addition to *cis*-2-butene also occurs, to give 70% of the *erythro-dl*-2-acetoxy-3-nitrobutane as shown below.<sup>13</sup> Since strong acid catalysts are known to cause rapid interconversion





of cis-trans isomers, nitrations of cis and trans-2-butenes promoted by sulfuric acid might be expected to give the same mixture of products. Instead, the stereochemistry of these reactions was found to be identical with that in the absence of strong acid.<sup>13</sup> The stereochemistry was determined by conversion of the products to 2-acetoxy-3-acetamidobutanes and comparison with authentic samples.

When o-xylene is treated with pure nitric acid in acetic anhydride, in addition to the expected 3- and 4-nitroxylens, 3,4-dimethylphenylacetate is formed and is the major product.<sup>10</sup> Other hydrocarbons also give rise to acetoxy products when they react with nitric acid in acetic anhydride, and it has been suggested that the acetoxyating species is protonated acetyl nitrate.<sup>10</sup> The most significant feature of the kinetic results obtained for the reaction of o-xylene with pure nitric acid in acetic anhydride is that the ratio of the yield of 3,4-dimethylphenylacetate to that of 3- plus 4-nitro-o-xylene is constant (0.72) when the rate of nitration is varied over a wide range by addition of either sulfuric acid, acetic acid, or lithium nitrate. One can conclude that either the same reactive species is responsible for both acetoxylation and nitration or that the separate acetoxyating and nitrating species must have a common precursor. This single reactive species, or precursor to separate species must effectively contain both an acetoxy and a nitro group and acetyl nitrate would seem the most obvious species. The following shows a typical product distribution with the percentage of acetoxylation indicated in parenthesis.<sup>10-12</sup>

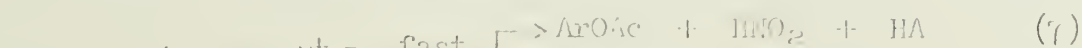
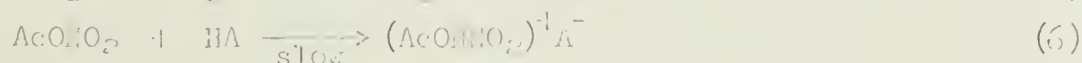


Fischer and co-workers have concluded that since pure nitric acid in excess acetic anhydride exists almost entirely as acetyl nitrate,<sup>24</sup> the latter cannot be the reactive species be-

cause the rates of both acetoxylation and nitration are zeroth order in o- and m-xylene.<sup>12</sup> If acetyl nitrate were the active entity, rates would be first order in both o- and m-xylene and nitric acid. It

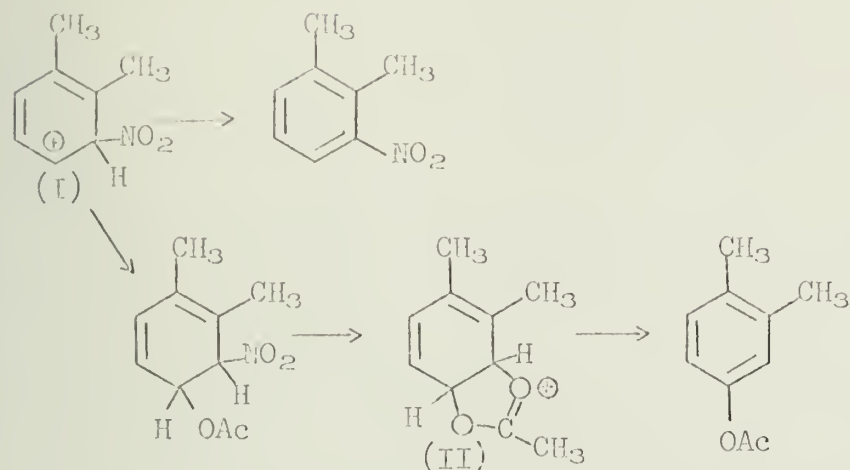
would appear, therefore, that acetyl nitrate is the precursor of the reactive species which must be formed in, or subsequent to, the rate-determining step. In view of the accelerating effect of sulfuric acid, the reactive species must be protonated, or formed from a protonated precursor, or formed in a protonation reaction. Therefore, an essential step would appear to involve reaction between acetyl nitrate and acid.

The above shows that the nitrating agent is being produced slowly in a step that does not involve the aromatic substrate. Fischer assumes that the acetoxylation is also an electrophilic substitution and then from the constancy of the ratio of acetoxylation to nitration, it appears to follow that the same intermediate is almost certainly responsible for both reactions.<sup>11</sup> He agrees with Bordwell in identifying this intermediate as protonated acetyl nitrate, for this species could act as both a nitrating agent and as an acetoxyating agent as shown in the following equations.





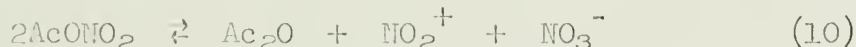
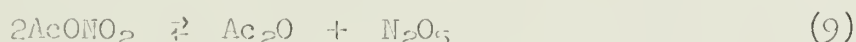
Paul has interpreted the above results in terms of nitration through nitronium ion.<sup>11</sup> Such a reinterpretation is possible if the acetoxylation is not an electrophilic substitution but an addition-elimination reaction. Such reactions are known to accompany some aromatic chlorinations<sup>12</sup> and de la Mare and Koenigsberger have pointed out that acetoxylation accompanying nitration may perhaps occur in the same way,<sup>13</sup> as shown in the following scheme. The rate determining step would be the slow



formation of the nitronium ion; this would then add to the aromatic substrate to give the carbonium ion (I). The insensitivity of the product ratio to added solutes could then be explained from the high reactivity of this carbonium ion. The absence of acetoxylation ortho to the methyl group can perhaps be explained from the lower acidity of the corresponding hydrogen atoms in intermediate II.

Paul has provided one key observation concerning the

mechanism of nitration by showing that the rate of nitration for benzene in acetic anhydride is repressed three-fold by a low concentration ( $10^{-3} \text{ M}$ ) of added sodium nitrate.<sup>14</sup> This could eliminate the possibility that acetyl nitrate or dinitrogen pentoxide are the effective nitrating agents, for the concentrations of neither of these species might be thought to be so sensitive to the concentration of nitrate ions. This can be seen from the fact that the concentration of acetyl nitrate is effectively equal to that of the added nitric acid, and the concentration of dinitrogen pentoxide in equilibrium with it as determined in equation 9. However, if the nitration occurs through the small concentration of nitronium ions provided by equation 10, the marked anti-catalysis of nitrate ion can be understood. From this Paul concluded that the nitronium ion was the intermediate involved in nitration in acetic anhydride.<sup>14</sup>



This conclusion was, of course, not accepted by Bordwell<sup>13</sup> or Fischer.<sup>12</sup> Bordwell explained the effect of nitrate ion by saying that it decreases the rate of reaction (relatively little temperature rise observed) and markedly increases the proportion of  $\beta$ -nitro nitrate. Fischer states that nitrate ion should compete with the aromatic substrate for protonated acetyl nitrate, and that nitrate ion can destroy this nitrating agent, not only by simple proton abstraction (eqn. 11) but also by formation of nitrogen pentoxide (eqn. 12). This is true when  $\text{A}^- = \text{OSO}_3\text{H}$ , however, when  $\text{A}^- = \text{NO}_3^-$  one would still expect the equilibria to shift to the right to a certain extent. Furthermore, an increase in concentration of the aromatic substrate should be accompanied by an increase in effectiveness of the substrate as a competitor for the protonated acetyl nitrate. Fischer's data show that addition of  $6 \times 10^{-4} \text{ M}$  lithium nitrate leads to a rate constant only one-twentieth of that observed in the absence of added nitrate, while the rate is halved when the xylene concentration is reduced to a fifth with the same concentration of lithium nitrate present.



Data for the nitration of aromatic compounds containing an ortho-para directing group suggests that if one uses acetic anhydride as the solvent instead of water, there is an increase in the proportion of ortho-substituted to para-substituted

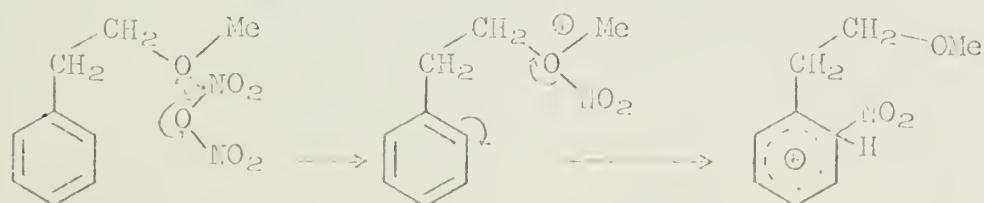


product.<sup>5</sup> The effect is well established for the nitration of anisole,<sup>3,4,6</sup> acetanilide,<sup>2,3</sup> and propionanilide,<sup>2,3</sup> but there is practically no effect in the case of toluene.<sup>7</sup> For anisole, an attempt has been made to account for the "ortho effect" on steric grounds.<sup>4</sup> If the nitrating agent in acetic anhydride is a molecular compound, such as acetyl nitrate, one can envision a mechanism whereby the directing group assists the incoming molecule, thus favoring substitution at the ortho position. The absence of a hydrogen-isotope effect in this position,<sup>4</sup> however, shows that displacement of the proton is not involved in the rate determining transition state. If the mechanism is electrophilic addition of nitronium ion,<sup>1,17</sup> as in aqueous solution, then a different explanation is possibly suggested, based on the polar character of the directing group and the dielectric constant of the solvent.

Paul has attributed the change in orientation to such an electrostatic effect.<sup>15</sup> In anisole, the dipole of the aromatic C-O bond has its negative end towards carbon, resulting in the ortho-positions being negatively polarized with respect to the para-position, while in chlorobenzene and bromobenzene the corresponding dipole is towards the halogen atom, making the ortho-position more positively polarized than the para-position. This produces an electrostatic attraction between the reagent and the ortho-carbon in anisole, aiding ortho-substitution, and a repulsion in the halogen benzenes, retarding ortho-substitution. In solvents of low dielectric constant this electrostatic influence is relatively more important, and Paul concludes that this may be one of the reasons for the observed change in orientation. Such a ground-state argument does not necessarily apply to what is actually occurring in the transition state. However, the isomer ratios obtained by Paul for the nitration of chloro- and bromo-benzenes,<sup>15</sup> are at variance with those obtained by other workers.<sup>18,29</sup> Also, his view that the electrostatic effect is enhanced in solvents of low dielectric constant is contraverted by the fact that the nitration of anisole in acetic acid, which has a lower dielectric constant than acetic anhydride, gives the same isomer distribution. Halvarson and Melander have suggested that the high ortho:para ratio might be due to initial attack of the nitrating species at oxygen, followed by an intramolecular rearrangement to the o-nitro compound.<sup>4</sup>

Norman and Radda have studied nitrations in acetic anhydride using methyl phenethyl ether as a model, since this compound contains an oxygen atom which is not bonded to the benzene ring.<sup>18</sup> It is also more suitable than anisole in that its reactivity in nitration is not likely to be complicated by nitrosation. They found that, as occurred with anisole and acetanilide, the ortho:para-ratio is considerably higher than in other solvents. Norman and Radda suggest that acetyl nitrate is not reactive enough to bring about nitration of the aromatic compound, and therefore gives rise to dinitrogen pentoxide which reacts in two ways.<sup>18</sup> It undergoes slow heterolysis to the nitronium ion which reacts with the aromatic compound to give o-, m-, and p-nitro-derivatives in the same proportions as when nitric acid is the reagent; and at the same time there is an additional mode of nitration at the ortho-position, dependent on the presence of the oxygen atom of the ether, and brought about by dinitrogen pentoxide.

The role of the oxygen atom must now be explained. Norman and Radda consider that nitration by dinitrogen pentoxide involves an Sn-2 type displacement in which the oxygen atom displaces nitrate ion from covalent dinitrogen pentoxide, giving a



a charged intermediate. This rearranges through a six-membered cyclic transition state to the usual  $\sigma$ -bonded intermediate of aromatic nitration and thence to the o-nitro-derivative.

This provides a route for the formation of the o-nitro-derivative which is



available neither at the para-position of the other, nor at the ortho-positions of ethyl benzene or toluene.

Several authors have reported high substrate selectivities in competitive nitrations of activated substrates by nitric acid in organic solvents.<sup>19,22</sup> Most noteworthy are the results of Dewar and his coworkers for a series of polynuclear compounds (phenanthrene, chrysene, benzo(a)pyrene, and anthanthrene) reacting with fuming nitric acid in acetic anhydride.<sup>33-35</sup> Thus for anthanthrene and diphenylamine rates of nitration of 116,000 and 738,000 relative to that of benzene have been reported.<sup>33</sup> Schofield's results for anthanthrene, as will be discussed below, would indicate that in Dewar's work the reaction observed was not nitration by nitronium ions.<sup>20</sup> Possibilities are the operation of a very much less reactive nitrating agent or of nitration through nitrosation as indicated in equation 13.



Schofield's data indicate a very great susceptibility of very active substrates to undergo nitrosation.

It is well established that especially reactive compounds such as phenols and phenolic ethers, and aniline derivatives, can be nitrated by a special mechanism (eqn. 13) in addition to that involving nitronium ions; they are first nitrosated and the nitroso-compound is then rapidly oxidized to the nitro-compound.<sup>37</sup> The anti-catalytic effect of nitrous acid upon the nitration by nitronium ion is replaced in the special mechanism by a markedly catalytic effect. The nitration of anthanthrene with pure nitric acid in sulpholan was practically instantaneous (<15 sec.), and Schofield says that such a result shows conclusively that under these conditions anthanthrene is not being nitrated by the nitronium ion mechanism since such nitration should have taken 15 minutes.<sup>20</sup> Also the rate of nitrosation increases with the concentration of nitric acid and the rates of reaction in the absence of added nitrous acid are very low.

Schofield has recently restudied the nitration of benzene and some more reactive compounds by solutions of acetyl nitrate in acetic anhydride at 25°.<sup>21</sup> The nitrating solutions were prepared from pure nitric acid and pure acetic anhydride. The data show that a limit to the rate of reaction is reached at about 10<sup>3</sup> times the rate for benzene. This limit, which Schofield takes to be the rate of encounter between the aromatic compound and the nitrating agent, is somewhat higher than has been observed in other media.<sup>19,20</sup> Of course, this difference could also be taken to indicate a change in mechanism.

Under the same conditions of reaction anthanthrene, diphenylamine, phenol, and resorcinol are nitrated 7 to 10 times faster than mesitylene. The reactions of these compounds are not always first order in concentration of aromatic substrate, and those of phenol and resorcinol are prone to autocatalysis. These observations relate to solutions prepared from pure nitric acid where [HNO<sub>2</sub>] < 10<sup>-4</sup> M. If the nitrating solutions are kept for several hours before use (during which nitrous acid is developed), or if fuming nitric acid is used in their preparation, the rates of nitration of these active substrates is enormously accelerated.<sup>21</sup>

The behavior of the very reactive substrates mentioned strongly suggests that nitration via nitrosation is accompanying another process of nitration associated with a limiting encounter rate. The possibility is still not excluded for the occurrence of nitration by an electrophile which is much less reactive, such as that suggested for olefins. It's interesting to note that no acetoxy-products have been cited in the literature for the nitration of highly activated substrates. Whichever explanation is correct, it is possible that there is at least a dichotomy in the mechanism of nitration for both very reactive compounds and those containing substituents capable of assisting in nitration. Unless the contributions of the separate mechanisms can be distinguished, quantitative comparisons of reactivity and ortho:para ratios are meaningless. In checking a literature reference for nitrations in acetic anhydride



one should very carefully note how the nitrating solution is prepared and under what conditions a particular substrate is nitrated.

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REACTIONS OF DIALKYL COPPER LITHIUM REAGENTS

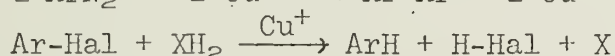
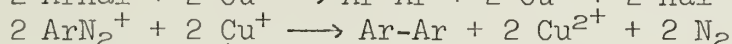
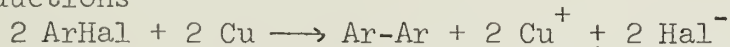
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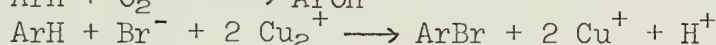
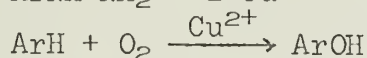
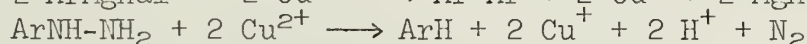
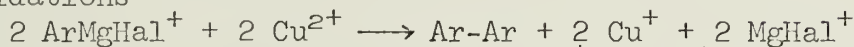
INTRODUCTION

Copper and organocopper compounds have long been studied as catalysts and reagents in many systems. Most of the initial studies were done in the aromatic series since Ar-Cu is more thermostable than R-Cu. The following are the most common examples:

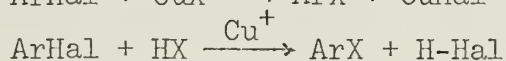
Reductions



Oxidations



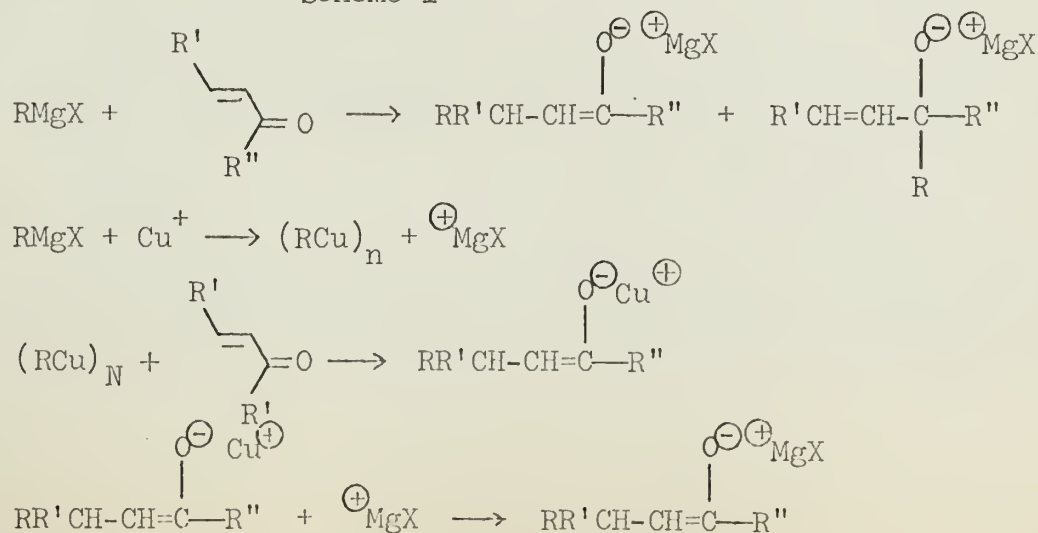
Replacements



The development of these reagents has to a large extent been empirical, however, a number of mechanisms of the reactions have been worked out.<sup>1</sup> Copper promoted reactions have been of recent interest in many areas of chemistry, ranging from biological systems<sup>2</sup> to applications in photochemistry.<sup>3</sup> No review articles covering all aspects of the effects of copper have been written, however, in 1965, Bacon and Hill summarized work done in copper catalyzed reactions in aromatic chemistry<sup>4</sup> and in 1966, J. E. Richmann reviewed reactions of organocopper compounds.<sup>5</sup>

One facet of the recent interest in organocopper chemistry has focused on the role of copper catalysts in promoting the conjugate addition of Grignard reagents to unsaturated carbonyl compounds.<sup>6</sup> From his studies of the reaction of *trans*-3-penten-2-one with Grignard and Grignard-like reagents, House postulated the existence of an organocopper species as a likely intermediate to account for the favored 1,4 addition product from this reaction (Scheme I).<sup>7</sup> To support this hypothesis several organocopper compounds were synthesized and their reactions were studied. As a result of this work attention was brought to the possible use of dialkylcopper lithium compounds as alkylating reagents.

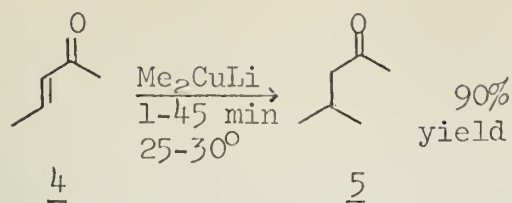
Scheme I<sup>7</sup>



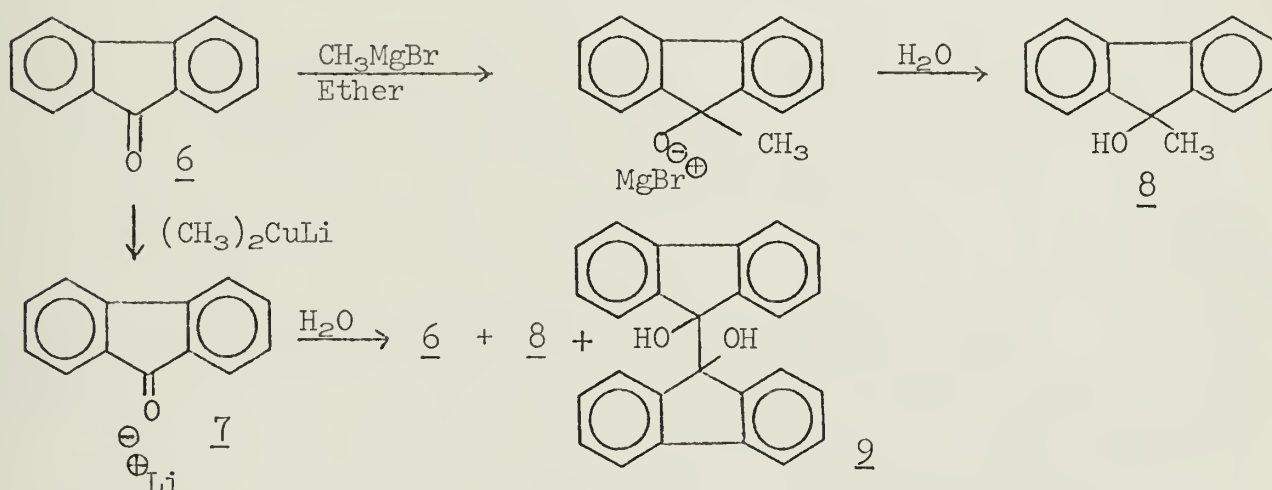
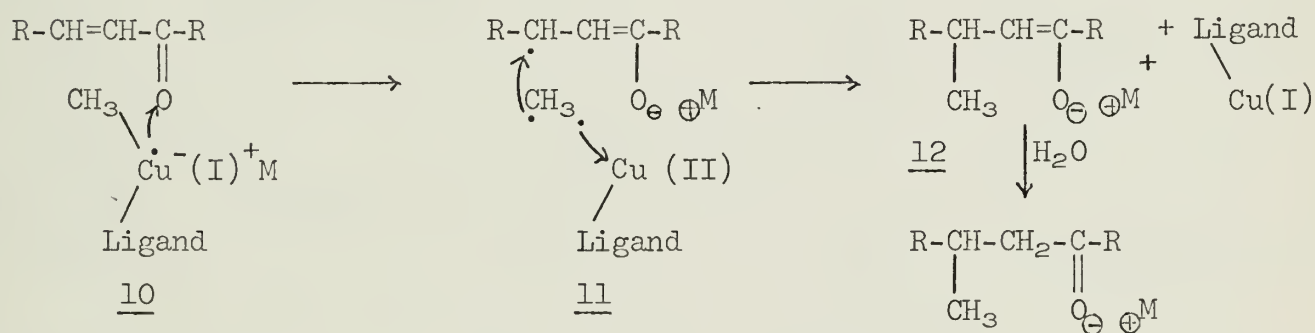








reaction of  $\text{Me}_2\text{CuLi}$  with fluorenone (6) in ether solution to indicate the presence of a radical anion as an intermediate in this type of addition (Scheme II).<sup>7</sup> Although addition of 6 to an ethereal solution of methyl magnesium bromide formed the alcohol 8 as the major product, the reaction of 6 with  $\text{Me}_2\text{CuLi}$  produced a solution which gave an esr spectra consistent with 7 and hydrolysis of this solution gave a mixture of 6, 8, and 9. While this does not prove that conjugate addition goes by a radical mechanism, it is consistent with the hypothesis that the conjugate addition of methylcopper (I) derivatives to  $\alpha,\beta$ -unsaturated ketones<sup>2</sup> proceeds via a one electron transfer (10) followed by transfer of a methyl radical as shown in Scheme III.<sup>7</sup>

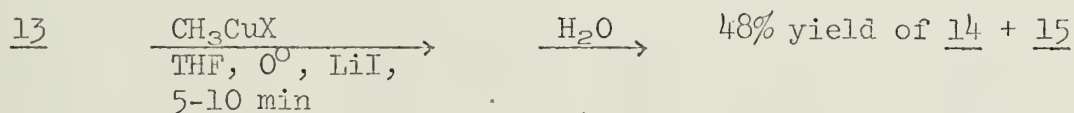
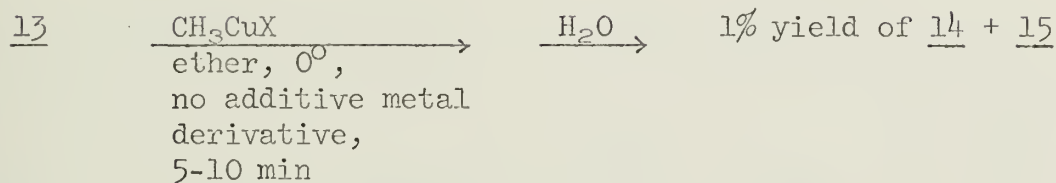
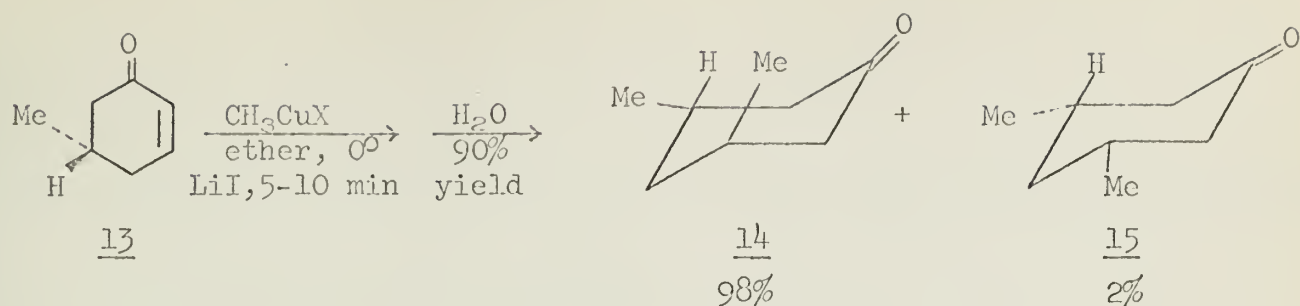
Scheme II<sup>7</sup>Scheme III<sup>7</sup>

Further investigation of the products obtained from the addition of methylcopper (I) derivatives to 5-methyl-2-cyclohexenone (13) (Scheme IV) established: 1) that methylcopper (I) derivatives prefer to attack the least hindered side of the conjugated ketone; 2) the necessity of having some other metal derivative present in solution to serve as an electron donor to copper in order for conjugate addition to occur as the major product; 3) that reaction in tetrahydrofuran (THF) is less efficient than in ether.<sup>7,12</sup>

In subsequent studies the primary concern with  $\text{Me}_2\text{CuLi}$  has been in its synthetic utility and it has been used in the key step of the synthesis of several natural products.<sup>13-20</sup> When these reactions were carried out at room temperature, diastereoisomeric mixtures are often formed in ca. 1:1 ratio<sup>13,14</sup> (Eq. 6-7), in some cases these mixtures were formed even at  $0^\circ$ .<sup>15</sup> However, the formation of compounds 16 and 17, intermediates in the synthesis of (+)-nootkatone<sup>16</sup> and

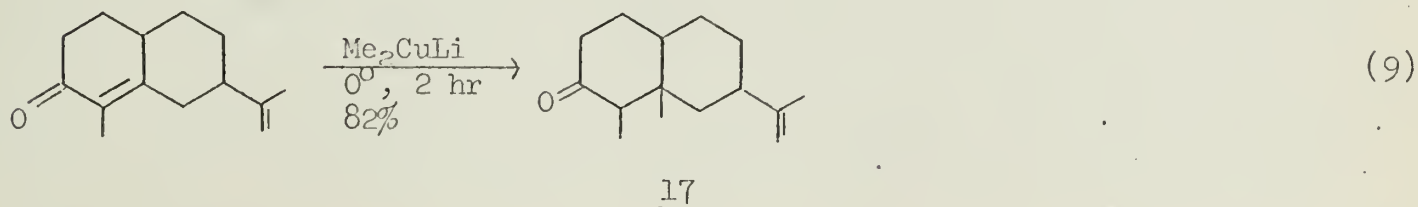
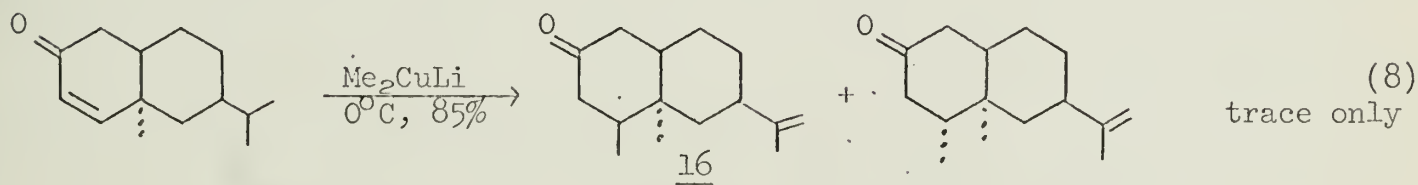
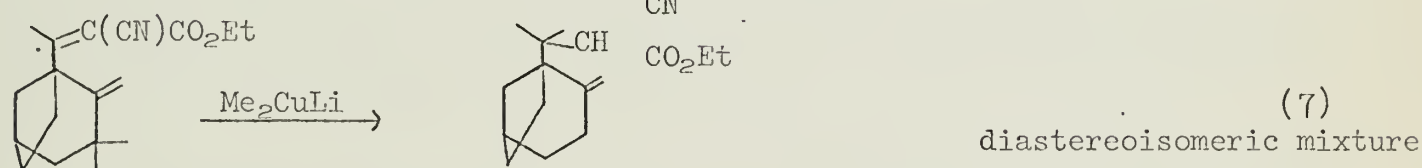
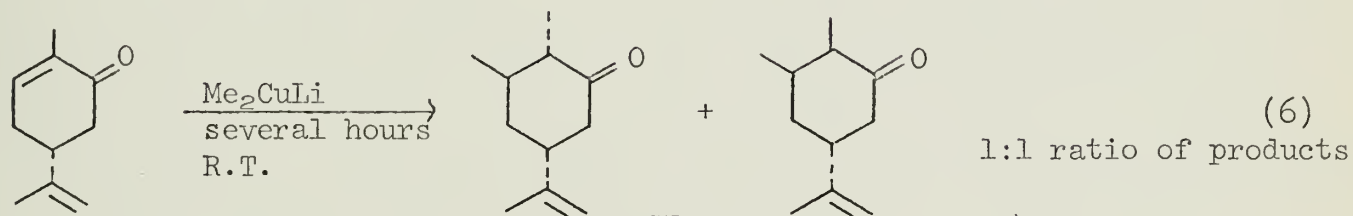


Scheme IV<sup>12</sup>



X = MeLi  
 LiPBu<sub>3</sub>,  
 LiP(OMe)<sub>3</sub>

(+)-eremophil-3,11-diene,<sup>17</sup> respectively, proceeds in a highly stereospecific manner (Eq. 8-9).

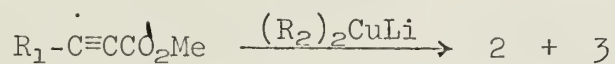




## CONJUGATE ADDITIONS: ACETYLENES

Studies on the conjugate addition of dialkylcopper lithium reagents to  $\alpha,\beta$  acetylenic esters (Eq. 3) have recently been carried out by three sets of workers. This reaction appears to provide a new and useful stereospecific synthesis of trisubstituted and tetrasubstituted olefins from readily available acetylenic precursors.<sup>21,22,23</sup>

The stereochemistry of the products formed in Eq. 3 is highly dependent upon the reaction temperature and the nature of the solvent, but seems to be independent of changes in  $R_1$  and  $R_2$  substituents (Table I). These studies,<sup>22</sup> as well as House's,

Table I. Stereochemistry and Yields of Conjugate Addition Products<sup>a</sup>

$R_1$	$R_2$	Solvent <sup>b</sup>	Temp (°C)	Time <sup>c</sup>	Additions <sup>d</sup>		Yield, <sup>e,f</sup> %
					$\underline{2}$	$\underline{3}$	
1.	$\underline{n-C_7H_{15}}$	$CH_3$	THF, ether	0	5 min	39 : 61	(90)
2.	$\underline{n-C_7H_{15}}$	$CH_3$	THF	-78	2.5 hr	99.8 : 0.2	95
3.	$\underline{CH_3}$	$\underline{n-C_7H_{15}}$	THF	-78	1 hr	100 : 0.0	90
4.	$\underline{n-C_7H_{15}}$	$\underline{CH_3}$	ether	-78	{ 5 min 2 hr	53 : 47 24 : 76	
5.	$\underline{CH_3}$	$\underline{n-C_7H_{15}}$	ether	-78	{ 5 min 3 hr	100 : 0 94 : 6	
6.	$\underline{n-C_7H_{15}}$	$CH_3$	toluene	-78	3 hr	92.5 : 7.5	(47) <sup>g</sup>

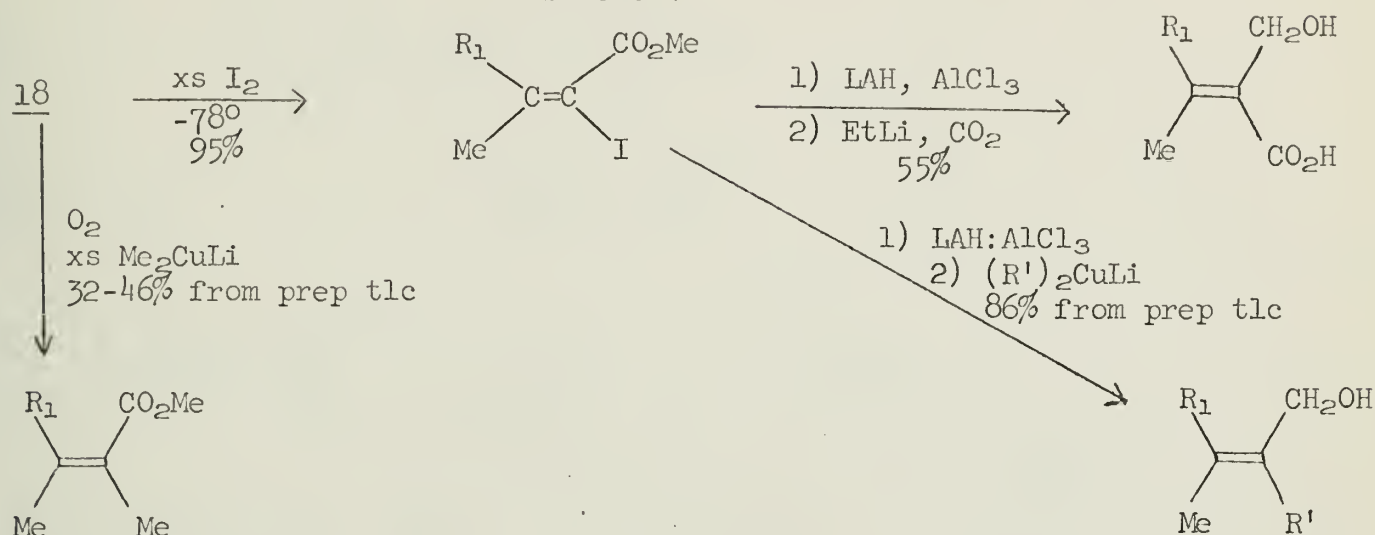
<sup>a</sup>All reactions were conducted under an atmosphere of dry nitrogen with rigorous exclusion of air and water. Aliquots were removed with syringes precooled to -78°, and reactions were quenched in methanol at -78°. Reactant stoichiometries were:  $R_1-C\equiv C-CO_2Me : R_2Li : CuI = 1 : 4 : 2-2.2$ . <sup>b</sup>Concentration was ca. 0.2 M in  $R_1$ . <sup>c</sup>Time was measured from time of mixing to time of quenching. <sup>d</sup>Isomer ratio was determined by gas chromatography. In each case where  $R = \underline{n-C_7H_{15}}$  the reaction was 100% complete; extent of reaction was not determined when  $R = \underline{CH_3}$  because starting material was too volatile. <sup>e</sup>Isolated yield; gas chromatographic yield in parenthesis. <sup>f</sup>Entries 1, 2, 4, and 6 also yielded a few per cent by-product; no contaminants were detected in entries 3 and 5. <sup>g</sup>Reaction was only 47% complete.

showed that a conjugate addition proceeds considerably faster in ether than in THF. Table I also reveals the predominant cis-addition product (the entering R group is cis with relation to olefinic H) yielded at low temperatures.

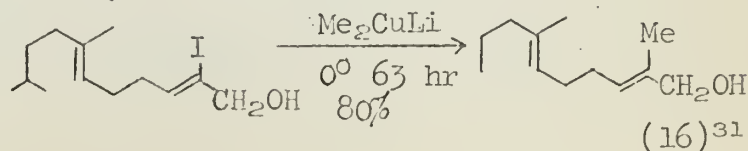
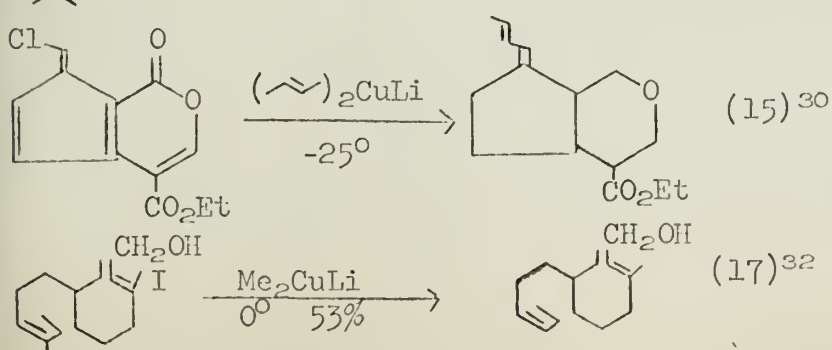
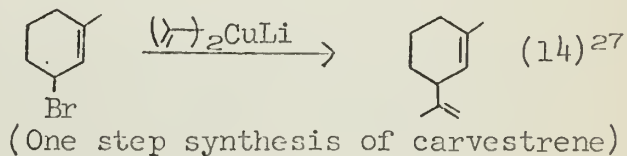
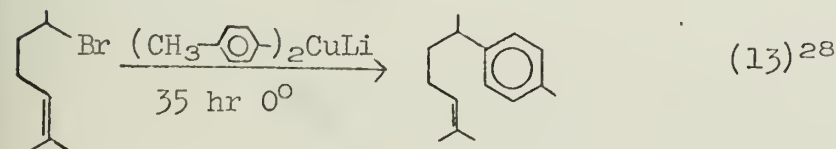
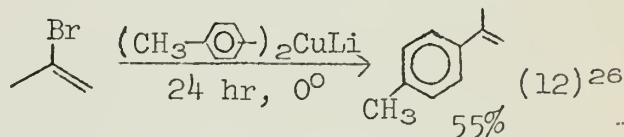
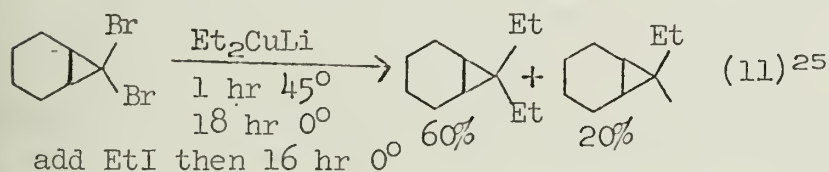
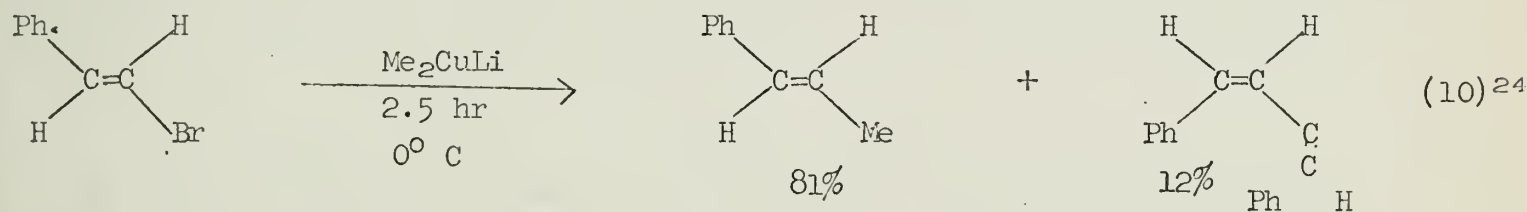
The mechanism for conjugate addition of copper reagents to  $\alpha,\beta$ -acetylenic esters is similar to that given in Scheme III. It is possible that a single molecule of  $RCu(I)$  complexes and donates successively an electron,  $R^\cdot$  and  $Cu(I)$  from one side. This would account for the predominance of the cis addition product. The occurrence of a mixture of cis/trans addition products can be explained by the equilibrium of enolates 18 and 19. Temperature and time of reaction were found to effect the position and rate of equilibrium, as shown in Table I. Also the addition of the electron donating ligands tetramethylethylenediamine or trimethylphosphate to the ethereal reaction mixture was found to greatly depress the rate of equilibration of the enolates.<sup>11</sup> From these data it is apparent that the greater the electron donating nature of the reaction environment, the less facile the equilibration between 18 and 19.



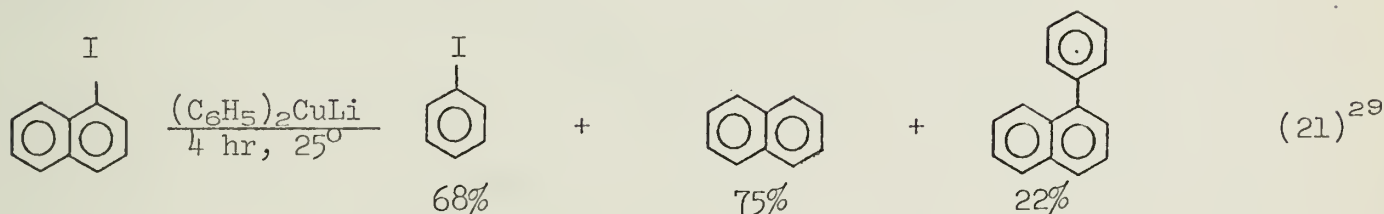
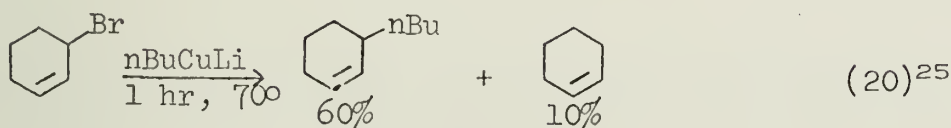
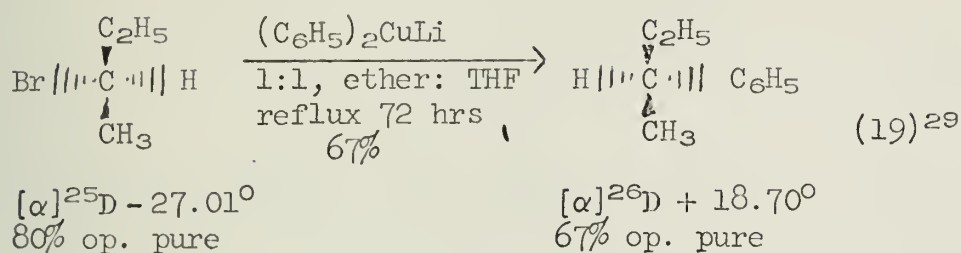
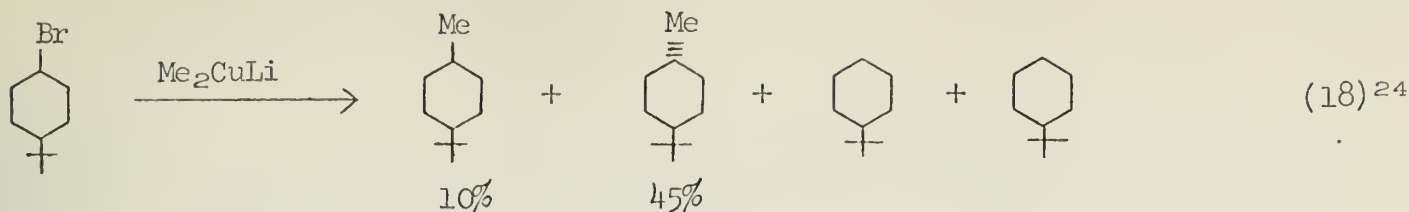
Scheme V



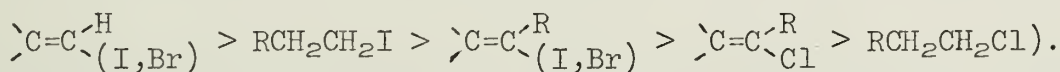
Dialkylcopperlithium reagents were also found to undergo reactions other than conjugate additions, particularly the replacement of halogen with an alkyl group (Eq. 4). Initially  $\text{Me}_2\text{CuLi}$  was used to affect the methylation of a number of compounds which other reagents such as  $\text{MeLi}$  had been unable to accomplish.<sup>24</sup> The scope of the reaction was quickly enlarged to include a large number of different alkyl,<sup>25</sup> vinyl,<sup>26,27</sup> and aryl<sup>28,29</sup> groups. Many previously long, difficult syntheses have been completed by the use of this reaction; Eq. 10-21 give a few examples and summarize experimental conditions.







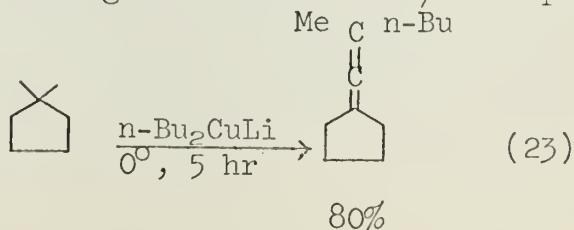
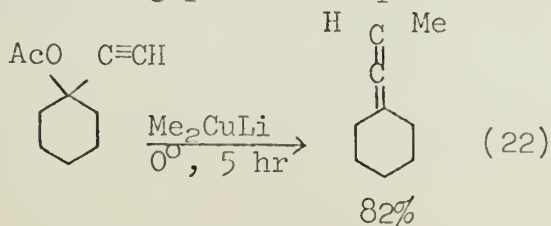
Presently very little is known as to the detailed mechanism by which these coupling products are formed, however, the predominant inversion of configuration at the carbon atom originally bonded to bromine in (19) would suggest a mechanism which involves an  $S_N2$  displacement.<sup>29</sup> From the applications to date some additional experimental generalizations may be made. Qualitatively dialkylcopper reagents react more rapidly than dimethylcopper, but as mentioned previously, they are less stable thermally. The optimum temperature range on these reactions tends to increase (ranging from  $-95^\circ$  to  $0^\circ$ ) with decreasing activity of the halide (approximate order:



Secondary halides are much less suited for coupling than are primary halides.<sup>25,29</sup> The principal side reaction of  $\text{R}_2\text{CuLi}$  with alkyl halides<sup>25</sup> and aryl halides<sup>29</sup> is due to replacement of the halogen by copper followed by protonation during the aqueous work-up (Eq. 12,<sup>13</sup> 21). In the case of the alkyl halide exchange can be nullified by a subsequent addition to the reaction mixture of an excess of the alkyl halide corresponding to the n-alkylcopper reagent. Elimination is another common side reaction.<sup>25</sup>

### $S_N2'$ DISPLACEMENTS

The third category of reactions which dialkylcopper lithium reagents participate in is the synthesis of alkylallenes in fair to high yield (65-85%) from substituted ethynylcarbinol acetates (Eq. 22-23).<sup>33</sup> Unfortunately no work has been completed correlating product composition and yield with changes in solvent and/or temperature.

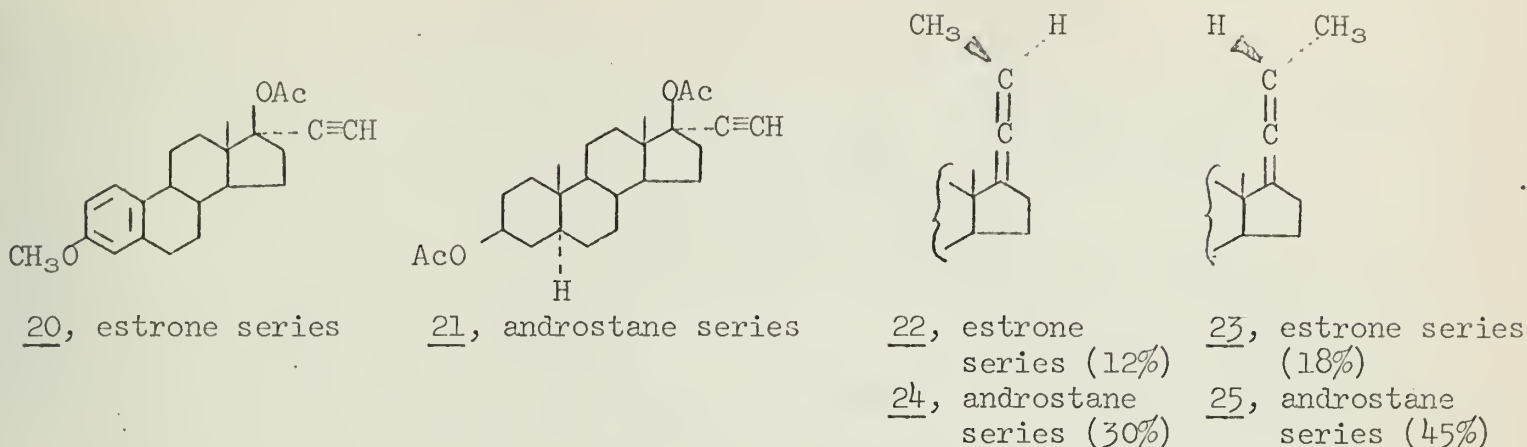


The importance of having acetate as the leaving group is indicated by the lack of formation of allenic material when hydroxyl is the leaving group or there is no leaving group.<sup>33,34</sup>

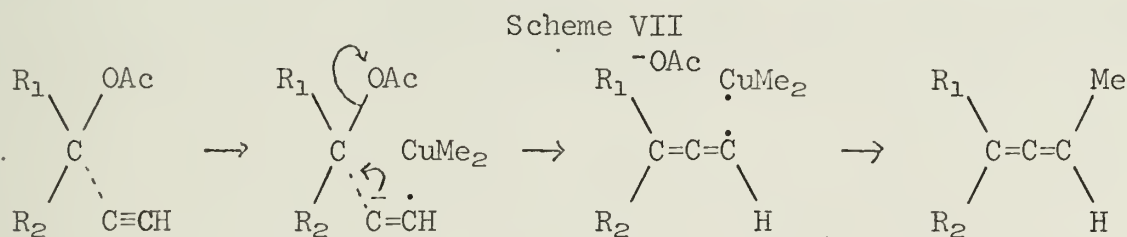


Reactions of steroidal ethynylcarbinal acetates 20 and 21 to form mixtures of their respective allenes 22, 23 and 24, 25 show that the reaction does not appear to be stereospecific (Scheme VI).

Scheme VI



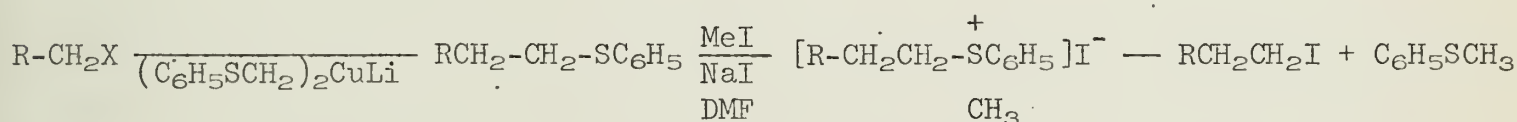
The proposed mechanism for this reaction is given in Scheme VII.<sup>33</sup> In this mechanism electron transfer of the methylcopper derivative to the acetylene is followed by expulsion of the acetate and transfer of the methyl radical.



## POSTSCRIPT

A unique method for the homologation of primary halides using a sulfur substituted copper reagent is outlined in Scheme VIII,<sup>35</sup> an indication that there may be many more applications in the use of dialkylcopper reagents in the field of synthetic organic chemistry.

Scheme VIII



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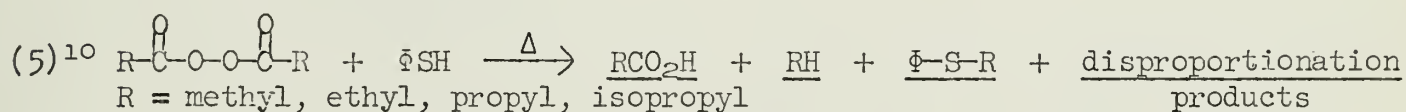
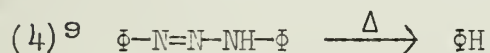
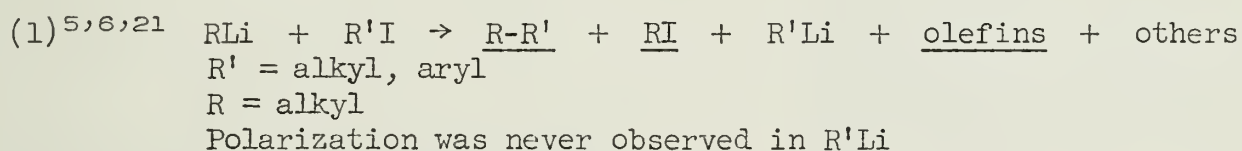
# THEORY AND APPLICATIONS OF CHEMICALLY INDUCED DYNAMIC NUCLEAR POLARIZATION

Reported by Ronald L. Muntz

November 17, 1969

In 1967 two research teams<sup>1,2,3</sup> discovered a phenomenon apparently related to the Overhauser effect or dynamic nuclear polarization.<sup>4</sup> They observed nmr spectra of products from rapid radical reactions. These spectra contained inverted peaks (emission) and peaks much larger than normal for the amount of material present (enhanced absorption). Since these results were caused by chemical rather than physical means, as in dynamic nuclear polarization, the phenomenon has been called chemically induced dynamic nuclear polarization (CIDNP). Polarization refers to a nonequilibrium distribution between energy levels. Many articles have followed the original reports describing similar results and advancing qualitative and some quantitative explanations. It will be the purpose of this seminar to discuss the types of systems and conditions giving rise to CIDNP, theories now used to explain CIDNP, and applications of CIDNP to organic chemistry. Emphasis will be placed on developments not covered in a brief review by Fischer and Bargon.<sup>4</sup>

Some typical reactions that give rise to CIDNP are listed (1)-(5). Products showing polarization are underlined; however, polarization of other products may not have been observable, owing to solvent interference etc., even though it may have occurred. These reactions were run in the spectrometer probe. Spectra corresponding numerically to reactions 1, 3, 4, and 5 are shown later.



Reactions (1)-(5) have in common, under the conditions employed, rapid rates (complete in a matter of minutes or seconds) and probable free radical intermediates. This suggests, along with the analogous Overhauser effect, that the mechanism giving rise to CIDNP involves coupling between the unpaired electrons and protons of the intermediate free radicals. The effect is noted in protons  $\alpha$  and  $\beta$  to the unpaired electron.

There now appear to be at least two mechanisms giving rise to CIDNP.<sup>11</sup> The first of these to be postulated was a direct analogy to the Overhauser effect and is more easily explained than is the more recent mechanism. In the initial mechanism, the simplest approach is to consider the intramolecular interactions of a proton coupled to the unpaired electron of a free radical (protons and electrons are known to have spin-spin coupling as evidenced by the hyperfine splitting in epr spectra).

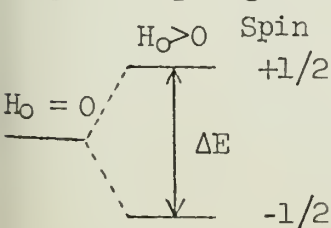


Fig. I. Energy Levels of an Electron or Proton

When a proton or an electron is placed within a magnetic field, its previously degenerate spin states separate forming two distinct energy levels (Zeeman levels; see Figure I). A Boltzman population distribution is established for the Zeeman levels; thus at thermal equilibrium the lower energy state is the more highly populated. When electromagnetic radiation is applied to the sample existing in a Boltzman distribution, net absorption takes place; since there is an excess of transitions from the lower to the upper level. However, if the population of the Zeeman levels can be altered so that the upper



Spectra corresponding to reactions 1, 3, 4, and 5.

(1)

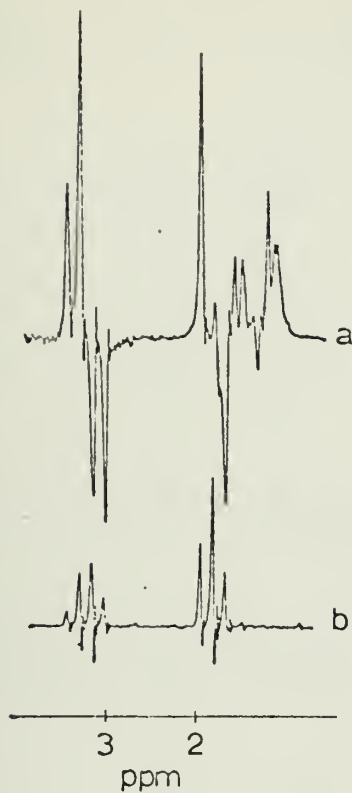


Figure 1. Reaction of ethyllithium with ethyl iodide in benzene. (a) Spectrum taken during the reaction, showing the methylene ( $\delta$  3.2) and methyl protons ( $\delta$  1.85) of ethyl iodide and butane ( $\delta$  1.0-1.6) (3.5-2.5-ppm region scanned with a spectrum amplitude twice that of the remainder of spectrum). (b) Reference spectrum of ethyl iodide.

(3)

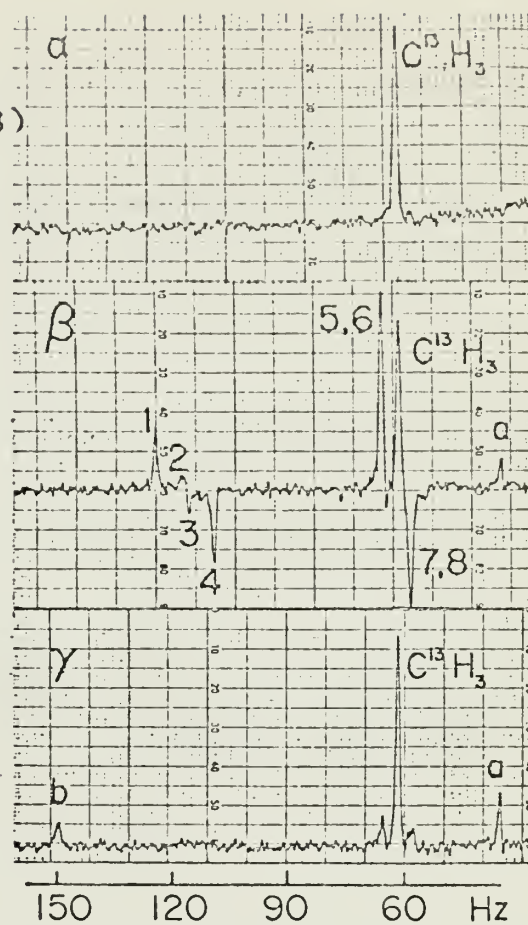


Figure 1. Nmr spectra of a solution of I (0.06 M) in toluene at 30°; ( $\alpha$ ) no light; ( $\beta$ ) light admitted; ( $\gamma$ ) after 10 min of irradiation. Chemical shifts are in hertz downfield from solvent  $\text{CH}_3$ .

(4)

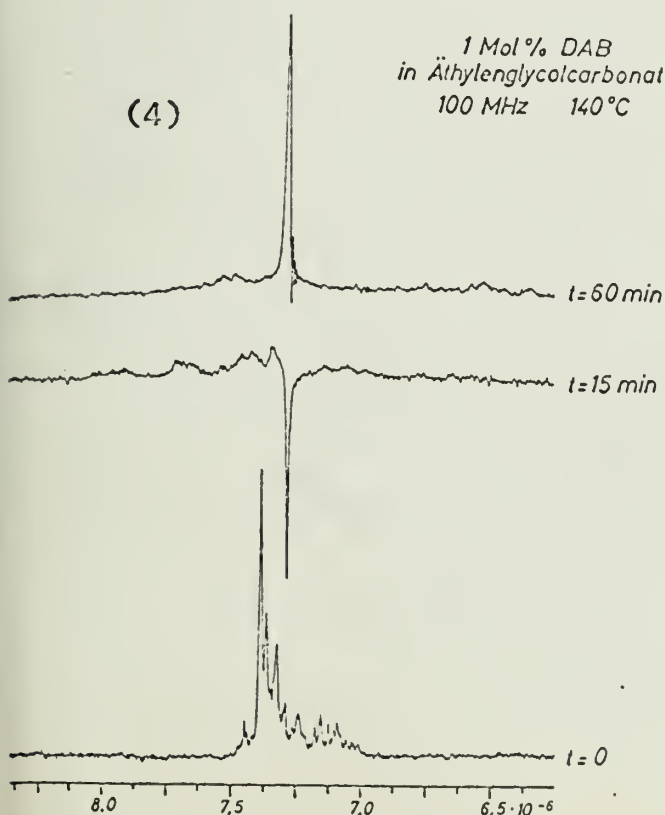


Abb. 1. Kernresonanzspektren während des Zerfalls von Diazoaminobenzol in Äthylenglycolcarbonat.

(5)

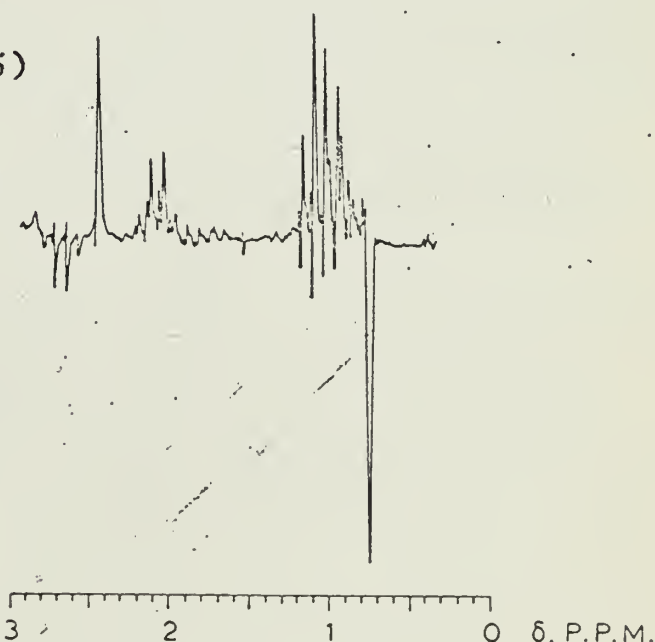


Fig. 1. The decomposition of dipropionyl peroxide in thiophenol.



level is more highly populated than the lower, emission will occur, giving signals appearing as inverted peaks.

The mechanism first proposed to account for deviations from the typical Boltzman distribution between the Zeeman levels considered the relaxation processes available to

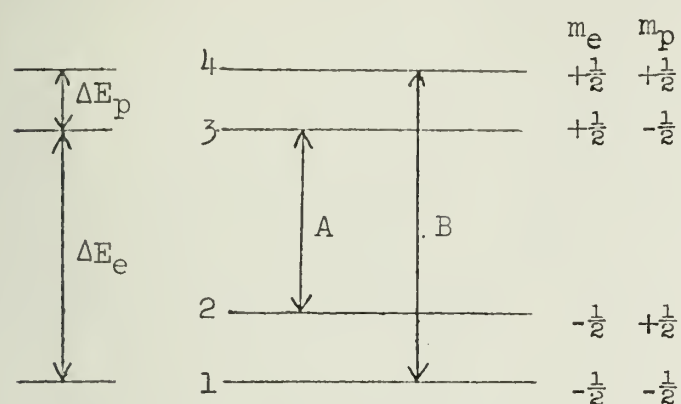


Fig. II.<sup>12</sup> Cross-Relaxation Processes in a One-Proton One-Electron System

electrons and protons. Relaxation consists of the processes by which electrons or protons try to arrive at and maintain a Boltzman distribution between the Zeeman levels. The relaxation method of interest involves coupled protons and electrons. A diagram representing the simplest such systems is shown in Figure II.

Transitions A and B in Figure II are termed cross relaxation processes since a spin flip in the electron is accompanied by one in the proton. In the case of dipolar coupling A will predominate while with scalar coupling B will predominate. If the population of the various Zeeman states are considered during the course

of a radical reaction, one possible mechanism of polarization becomes apparent and was postulated by both of the original research teams.<sup>1,2</sup>

In Figure III step "a" is homolysis of the C-Y bond and is assumed to give equal populations in the electronic Zeeman levels at "A". Process "b", which will occur if

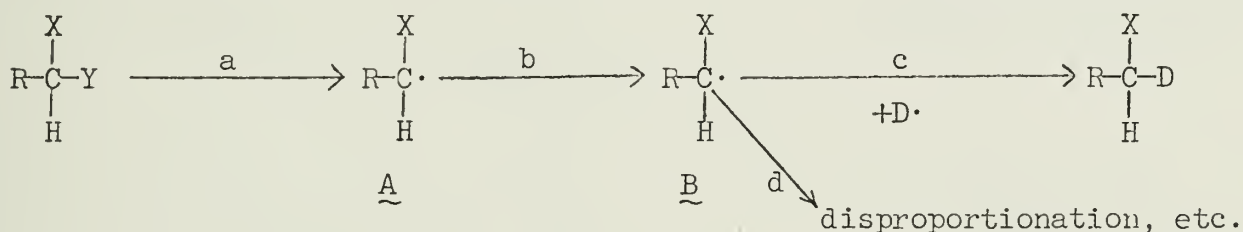


Fig. III. Steps in a Radical Reaction

the reaction is carried out in a magnetic field, is relaxation of the unpaired electrons of the radical to a Boltzman distribution, this being the stable state of the radical in a magnetic field. If the protons of the radicals are coupled to the unpaired electrons, as in Figure II, relaxation of the unpaired electrons in "b" causes protons to undergo concomitant transitions resulting in an overpopulation of upper or lower proton Zeeman levels. Dipolar coupling gives overpopulation of the upper proton levels resulting in emission while scalar coupling results in the opposite polarization and enhanced absorption. For this type of polarization to occur, the radical must live long enough to allow the protons to become polarized but not long enough for them to relax to a Boltzman distribution. Estimates<sup>3,10</sup> of the necessary lifetime for observable polarization range from  $10^{-4}$  to  $10^{-10}$  sec. This type of polarization has been termed "longitudinal polarization" by Closs.

Until Closs's recent work,<sup>8</sup> process "b" in Figure III was the only point in the radical reaction purported to give polarization; however, Closs has pointed out a new site in the reaction sequence where polarization can take place in addition to a totally new mechanism to account for facts unexplainable by the old (longitudinal) mechanism. The new proposed step leading to polarization is after B; the unpaired electrons are in a Boltzman distribution, and when product formation ("c" or "d") takes place, the electrons must be paired with another electron thus requiring an excess of transitions from the lower to the upper state. This should give the opposite polarization as process "b". Closs's reason for proposing polarization at the product forming stage was data from reaction (3). This reaction involves hydrogen abstraction by diphenylmethylene; however, it was shown<sup>9</sup> that the triplet diphenylmethylene relaxes to a Boltzman distribution faster than it abstracts hydrogen atoms. Since the abstracted hydrogens showed polarization, this must have occurred at some later stage in the reaction; the most logical place being product formation.

The amount of polarization is defined<sup>8</sup> by  $(\langle I_z \rangle - \langle I_z \rangle_0) / \langle I_z \rangle_0$ ; where  $\langle I_z \rangle$  and  $\langle I_z \rangle_0$  are respectively the expectation values of the nuclear spins in the polarized states and



at thermal equilibrium. The polarization is determined experimentally by using the unpolarized peak area as  $\langle I_Z \rangle_0$  and the polarized peak area as  $\langle I_Z \rangle$ .

When polarized spectra are examined in detail, two additional facts cannot be explained<sup>11</sup> by the longitudinal polarization mechanism. First, the observed polarization may be greater than  $\gamma_e/\gamma_n = 660$ ; where  $\gamma_e$  and  $\gamma_n$  are the magnetogyric ratios of the electron and proton respectively. Longitudinal polarization theory requires that the polarization be less than this value. Second, the integral over the spectrum may be equal to zero, to a first approximation; that is, the number of protons with positive spin is approximately the same as those with negative spin, a direct contradiction to the longitudinal mechanism. One manifestation of the overall zero integral is the so-called multiplet effect in which the integral over a multiplet is approximately zero, *i.e.*, part of the peaks in the multiplet show enhanced absorption while others in the same multiplet show emission. In order to explain these two facts Closs has espoused an entirely new mechanism (so-called "transverse polarization").<sup>14</sup>

An explanation of how the multiplet effect arises can be seen by correlating allowed transitions in the energy diagram of an AB system (Figure IV C) with the peaks in an AB spectrum.

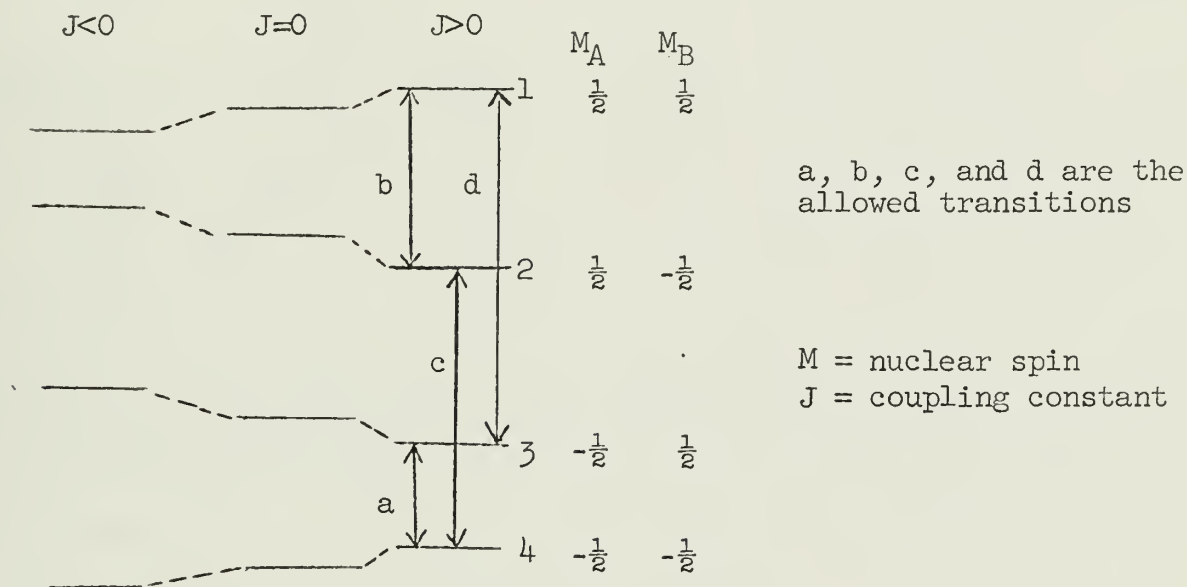


Fig. IV C.<sup>13</sup> Proton Energy Level Diagram for an AB System

Figure IV D represents the normal, *i.e.*, no CIDNP, AB spectrum with peaks labeled to correspond to the transitions in Figure IV C. If energy levels 1 and 4 in Figure IV C become overpopulated by some polarization mechanism, the resulting spectrum would resemble that shown in Figure IV E; conversely, if energy levels 2 and 3 became overpopulated, the spectrum would appear as in Figure IV F. Figure IV F corresponds to the spectrum obtained in reaction (3) for the methine protons of  $\phi\text{CHCH}(\text{CO}_2\text{CH}_3)\phi$ . Thus in this triplet reaction, if one assumes a positive vicinal coupling constant, energy levels 2 and 3 must be overpopulated by some polarization mechanism.

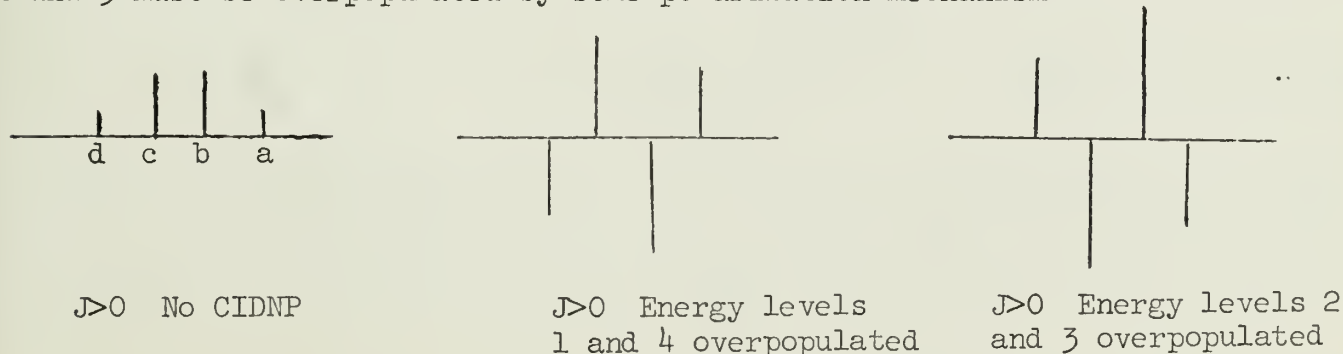


Fig. IV D

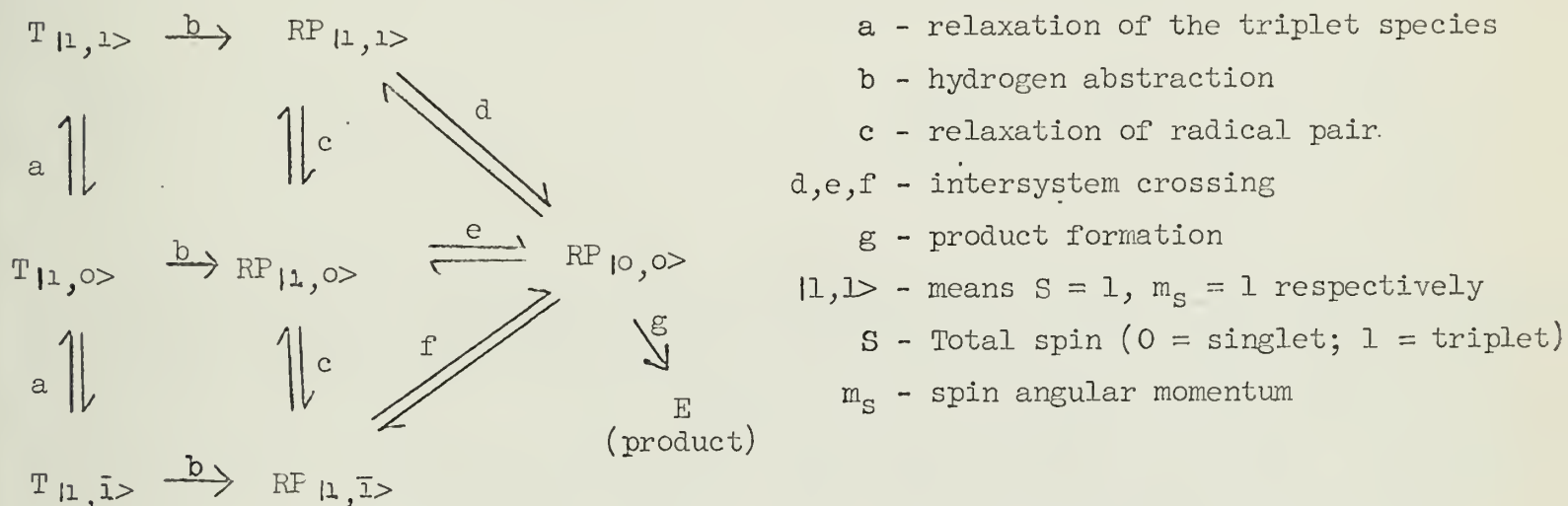
Fig. IV E

Fig. IV F



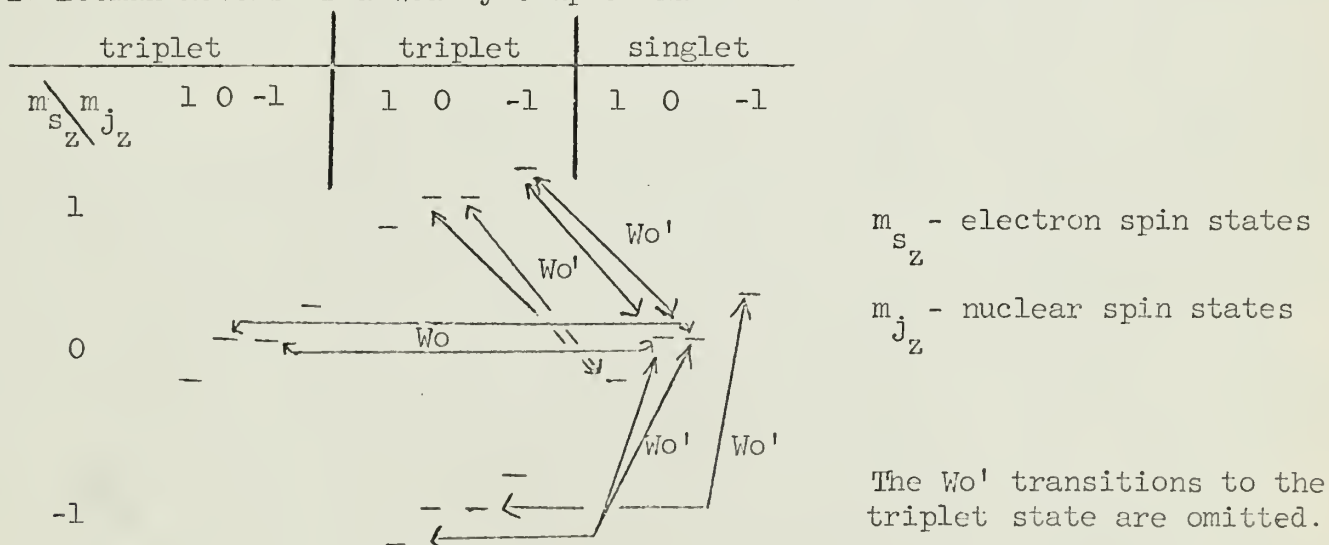
The explanation of Closs's "transverse" mechanism for the observed multiplet effect in radical combination reactions involves Figure V and Figure VI. He presents a quantum mechanical explanation of the mechanism;<sup>14</sup> however, only a qualitative explanation will be attempted here. Much of the theory Closs employs is more fully discussed in a recent review of dynamic nuclear polarization.<sup>15</sup> Figure V represents the stages in a triplet reaction where the original triplet species (T) abstracts a hydrogen atom forming a radical pair (RP) which goes on to form product (E). Since relaxation ("a") of the triplet  $\dot{\Phi}_2C$  is much faster than hydrogen abstraction ("b"), as previously noted, one must look to later steps in the reaction ("d", "e", or "f") to explain the observed polarization.

Fig. V. Radical Reaction Sequence Including Electron Zeeman States



According to Closs's theory the population of the states given in the matrix of Figure VI depends on the orientation and separation of the radicals in the radical pair since this causes the magnitude of coupling between the radicals to vary. If one then looks at the populations of these states over a period of time, they will fluctuate as

Fig. VI. Zeeman levels of a Weakly Coupled Radical Pair with Two Protons



the radicals change positions relative to each other, causing apparent transitions ( $Wo$  and  $Wo'$ ) between the energy states. Closs presents a quantum mechanical argument that the process  $Wo$  is much faster than  $Wo'$ ; the driving force being electron pairing in product formation. Since  $Wo$  connects the Zeeman proton levels with spin closest to zero in the singlet and triplet states,  $RP |0, 0\rangle$  will be populated more rapidly in the nuclear Zeeman levels near zero and will transmit this polarization to the product.

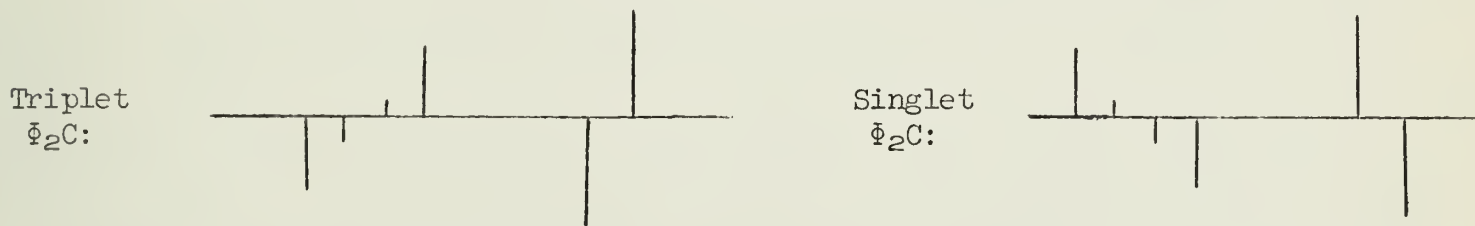
This mechanism correctly predicts observed multiplet effects in radical combination reactions; it also, in theory,<sup>11</sup> could bring about polarization magnitudes greater than  $10^4$  (i.e., greater than  $\gamma_e/\gamma_n$ ). These are the two facts not explained by the longitudinal mechanism. Another interesting prediction made from this mechanism is that the



polarization due to singlet intermediates will be opposite to that of the same reaction involving triplets. This prediction was made as follows: In the singlet reaction,  $RP_{10,0}$  is formed directly by hydrogen abstraction; however, some of  $RP_{10,0}$  may undergo intersystem crossing forming the triplet radical pair. Since, from Figure VI, this will occur most rapidly from the nuclear Zeeman levels nearest zero, an overpopulation will be left in  $RP_{10,0}$  in the levels farthest from zero which will again be transmitted to the product. This corresponds to the opposite polarization as that from the triplet precursor.

This prediction was checked<sup>18</sup> by generating singlet  $\Phi_2C:$  in reaction (3). The observed polarizations were, in fact, opposite giving interchanged emission and enhanced absorption lines (see Figure VII).

Fig. VII. Portions of the Spectra of Polarized 1,1,2-Triphenylethane

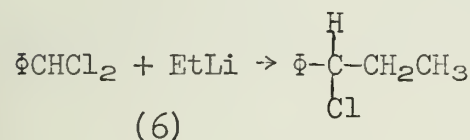


The two mechanisms postulated thus far explain much of the data now available; however, there are still some results which are difficult to explain. For example, in Ward and Lawler's original work,<sup>1</sup> in order to see polarization in the reaction of *n*-butyllithium with *n*-butylbromide it was necessary to add a compound containing carbon-carbon unsaturation.

Also, if 2-pentyne replaced diphenylacetylene as the unsaturated compound, the emission and absorption peaks were inverted. A plausible explanation for this might be a change in radical lifetimes so that in one case polarization occurs during the radical relaxation to a Boltzman distribution while in the other it occurs during radical pairing of product formation.

An even more disturbing experimental result was presented in Ward and Lawler's latest communication.<sup>16</sup> In this communication "zero-field polarization" was reported.

That is, CIDNP was observed in reaction products even when the reaction was complete before the sample was exposed to a magnetic field. One reaction in which this effect is observed is (6). Not only is the appearance of this polarization unexpected, since the Zeeman levels are degenerate in zero field, but also the polarization may be opposite (i.e.



emission changes to absorption and vice versa) to that observed in the same reaction carried out inside the spectrometer probe. No theory has yet been postulated to account for these observations. Essentially, zero-field polarization requires splitting of the spin levels by electron-electron or electron-nuclear interactions taking place during the radical reaction (possibly like Closs's mechanism). How these zero-field processes effect polarization in the sample when placed in the spectrometer is unknown. It is interesting to note that magnitudes of polarization decrease with increase in magnetic field<sup>17</sup> and it is possible that zero field polarizations might have the largest possible magnitudes. Mechanisms to explain multiplet effects in reactions other than radical combinations are now being investigated by Kaptein.<sup>14</sup> An important step in these studies, in addition to basic explanatory theory, is a method of obtaining the concentration of the polarized species; at present an empirical method has been developed to accomplish this.<sup>24</sup>

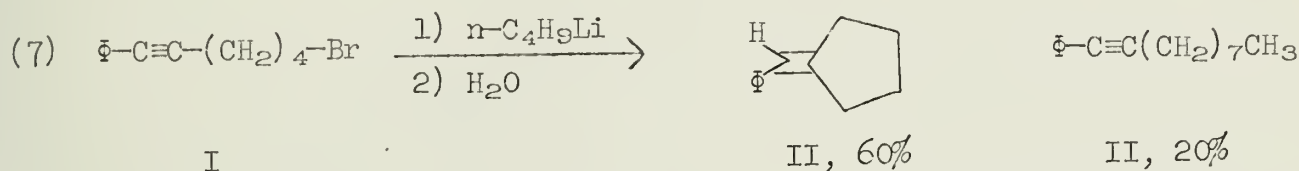
As is the case with many physical tools, CIDNP can be useful without being fully understood. As stated previously, CIDNP can be used to differentiate between singlet and triplet radical coupling reactions<sup>18</sup> when the sign of the vicinal coupling constant is known. Conversely, if the multiplicity of the reacting species is known the sign of the coupling constant can be deduced.

A more general application of CIDNP is the determination of the radical character of reactions. Two things should be noted about this: first, observations of CIDNP does not prove that the reaction proceeds entirely by a radical mechanism; and second, the absence of CIDNP does not rule out a radical mechanism.



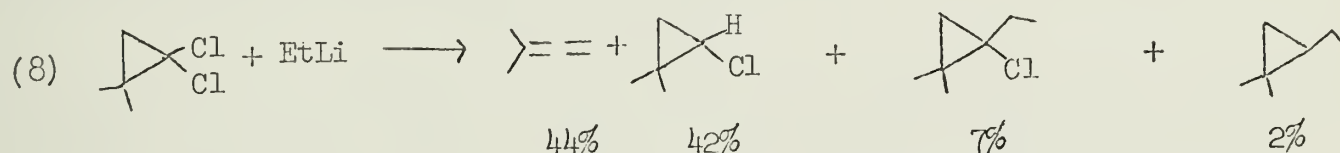
Several examples employing CIDNP to identify radical mechanism have appeared in the literature. A few of these follow:

Ward studied<sup>1</sup> the cyclization of acetylenes (7). Kandil and Dessey had previously proposed<sup>19</sup> an aryllithium intermediate, carbanionic mechanism for a similar reaction; however, polarization of the vinyl proton of II indicates a radical mechanism, at least in part.



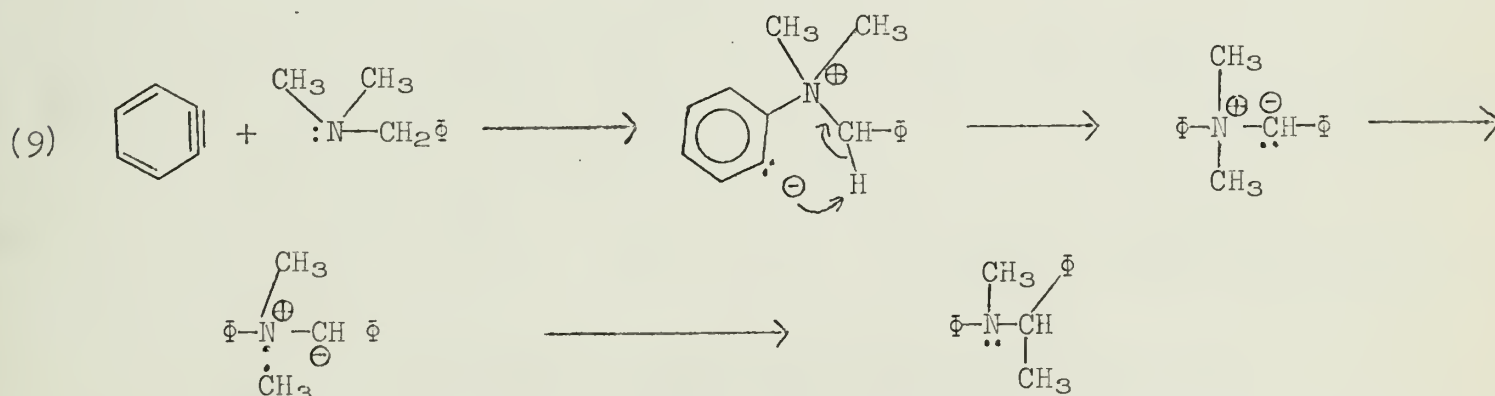
A more controversial reaction mechanism is that of lithium-halogen interchange reactions. Applequist and O'Brien originally interpreted the exchange as an ionic reaction. However, it has been shown<sup>5,6,21</sup> in the case of alkyl and aromatic iodides that the iodide exchange product exhibits polarization and must come, in part, from a radical intermediate. In the case of other alkyl halides, i.e., chlorides and bromides, CIDNP has been observed for some reaction products but not the exchange products.<sup>20</sup> Thus, there is still no evidence for a radical mechanism in the exchange of these halides.

Another interesting reaction<sup>22</sup> is that of 1,1-dichlorocyclopropanes with alkyl-lithium reagents (8). Both major products of this reaction show polarization; the authors use this as evidence to support the intermediacy of a 2,2-dimethyl-1-chlorocyclopropyl radical.

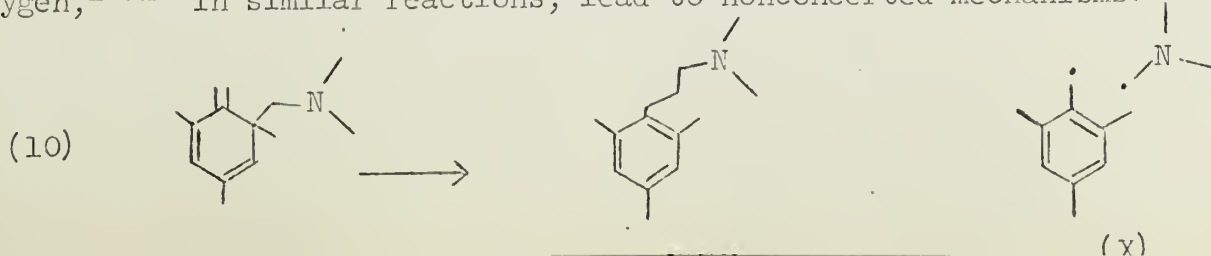


CIDNP has also been observed in the cleavage of 2-tetrazenes,<sup>23</sup> suggesting a homolytic rather than heterolytic cleavage.

The addition of benzyne to N,N-dimethylbenzylamine gives mainly N-methyl-N-( $\alpha$ -phenethyl)aniline. The benzylic methine of the product show polarization indicating a free radical precursor.<sup>25</sup> The following mechanistic scheme is suggested (9).

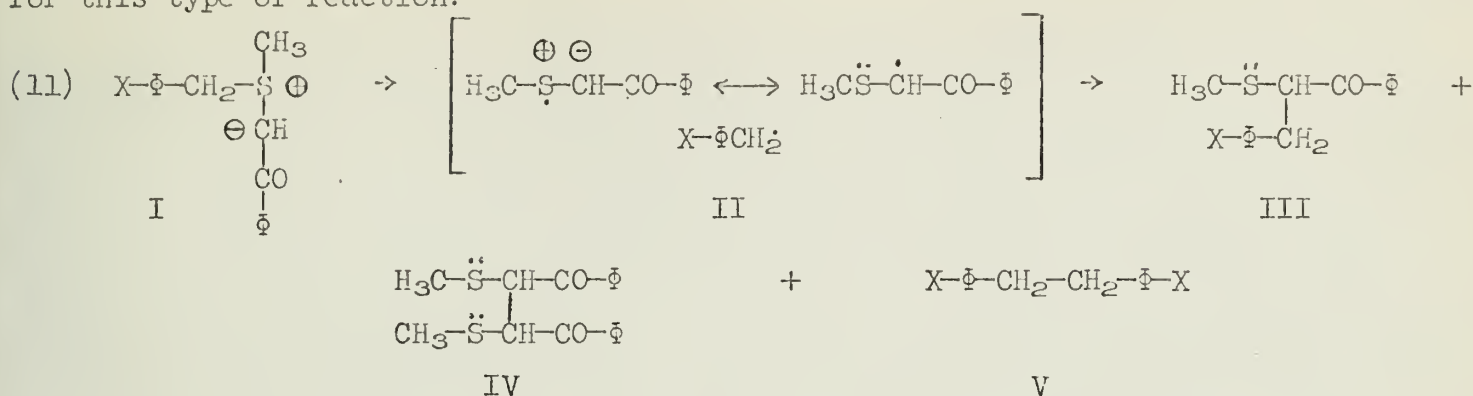


Prediction of the geometry of sigmatropic shifts by orbital symmetry arguments is possible if the reaction is concerted; however, if the reaction is not concerted, these predictions are not theoretically feasible. Baldwin and Brown report<sup>26</sup> that the 1,3-sigmatropic reaction shown in (10) gives polarized spectra and therefore proceeds via a radical rather than concerted mechanism. The authors suggest a radical pair intermediate (X). This radical reaction agrees with previous results that sulfur<sup>27</sup> and oxygen,<sup>28,29</sup> in similar reactions, lead to nonconcerted mechanisms.

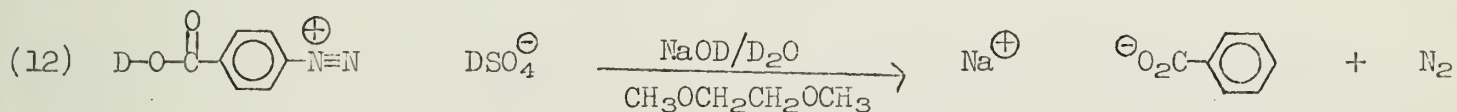




CIDNP has also been observed in the products of the decomposition of methyl-benzyl-phenacyl-sulfonium-ylide<sup>30</sup> (11) and in the closely related Steven's rearrangement of benzyl-dimethyl-phenacylammoniumylid.<sup>31</sup> Ionic mechanisms have usually been postulated for this type of reaction.



The Meerwein reduction of aromatic diazonium salts (12) shows CIDNP in the form of emission peaks in the aromatic region of the product spectrum.



Although most applications of CIDNP have involved coupling of protons and electrons; it has recently been reported<sup>9</sup> that fluorine atoms may also be affected by CIDNP.

With the widening scope and better understanding of this recently discovered phenomenon, CIDNP most certainly will play an important role in future mechanistic studies of reactions involving paramagnetic intermediates.

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Reported by Fred S. Fry, Jr.

November 20, 1969

The chemiluminescence of many different types of organic compounds has been investigated in the recent literature. Much of the work has been done in order to determine the mechanisms of certain bioluminescent reactions, which are oxidations by molecular oxygen of some substrate called a luciferin, and which are catalyzed by an enzyme called a luciferase. Chemiluminescence studies have been done on the luciferin compounds themselves, but they are usually done on a simpler model compound which has certain structural similarities to the luciferin. In general, these reactions have been shown to involve the formation of an adduct between oxygen and the anion of the compound in question. This adduct then forms a four-membered cyclic peroxide which can decompose in such a manner as to give an electronically excited species, which returns to the ground state by emitting a photon whose energy generally is in the visible light region. Four-membered cyclic peroxides have also been suggested as possible intermediates in the chemiluminescence of compounds derived from oxalic acid.

Bioluminescent reactions proceed by deprotonation followed by a reaction with molecular oxygen at an enzyme site to form an adduct which eventually reacts to emit radiation. Hopkins and coworkers<sup>1</sup> report that in the oxidation of D-firefly luciferin, the stoichiometry is 1:1 with oxygen and that hydrogen peroxide is not a product. Reactions of this type occur with the typically high efficiencies of enzyme-catalyzed reactions, as noted in the *in vivo* reaction of firefly luciferin with a quantum efficiency of 0.88 for the yellow-green emission at 565 nm.

Most chemiluminescent reactions in simple systems have been found to proceed with very low efficiencies when done in aqueous media. Seliger<sup>2</sup> found that the chemiluminescent reaction of luminol in an  $\text{H}_2\text{O}/\text{H}_2\text{O}/\text{NaOH}/\text{NaOCl}$  system at (optimum)  $\text{pH} = 11$  had a quantum yield of about 0.02 (the highest for an aqueous system so far). White<sup>3</sup> showed that when chemiluminescence reactions were carried out in weakly acidic, aprotic organic solvents such as dimethylsulfoxide (DMSO) or dimethylformamide (DMF), they required only base and molecular oxygen, and in general they were more efficient than reactions on the same compound in an aqueous medium. Seliger<sup>2</sup> showed that the luminol reaction had a quantum yield of about 0.1 in  $\text{DMSO}/t\text{-BuO}$ . Most of the current work in chemiluminescence has been done using these organic solvent systems in which a base stronger than hydroxide may be used.

#### MECHANISMS OF OXIDATION

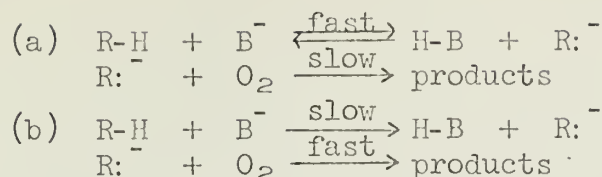
The first step in the oxidation phase of a chemiluminescent reaction is the removal of an acidic hydrogen by base from either nitrogen<sup>4</sup> or carbon.<sup>5</sup> This carbanion then reacts with molecular oxygen to form an adduct. Russell<sup>6</sup> reported that these reactions often involve radicals, and so the ability of some compound, R-H, to be oxidized depends on not only the rate of deprotonation but also on the relative stabilities of the carbanion,  $\text{R}^-$ , and the radical,  $\text{R}^\cdot$ , which influence the rate of electron transfer.  $\text{R-H} \rightarrow \text{R}^-$ ;  $\text{R}^- + \text{X} \rightarrow \text{R}^\cdot + \text{X}^-$  where X is some electron acceptor, and may be  $\text{O}_2$ . Much of Russell's work has been done on three systems: 9-substituted fluorenes,<sup>7</sup> triphenylmethane,<sup>7-9</sup> and diphenylmethane.<sup>7,9</sup>

Fluorene protons are more acidic than those of triphenylmethane and diphenylmethane, and its oxidation has been shown to follow Scheme Ia. Fluorene in *tert*-butyl alcohol (or DMSO) and base is in equilibrium with its anion, while the rate-determining step in the oxidation is the reaction with  $\text{O}_2$ . Addition of *m*-trifluoromethylnitrobenzene, which accepts one electron from the anion, greatly increases the rate of  $\text{O}_2$  uptake, and the rate of this catalyzed oxidation follows the rate of electron transfer measured by ESR spectroscopy in the absence of oxygen.<sup>7</sup> This is in keeping with the postulate that electron transfer and radical intermediates are involved in the overall process, and it establishes a chain mechanism such as the one

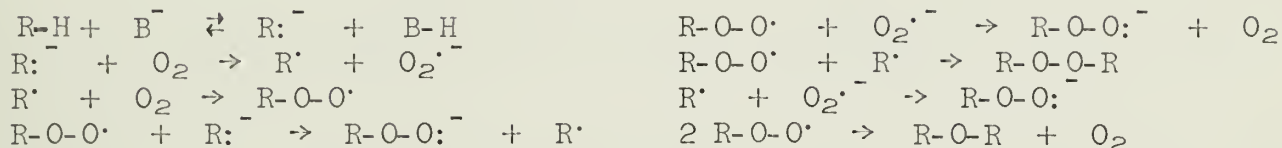


in Scheme II.<sup>7,8</sup>

#### Scheme I

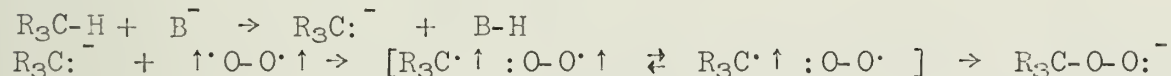


#### Scheme II



The triphenylmethane and diphenylmethane are less acidic than the 9-substituted fluorenes, and their oxidation has been shown to follow Scheme Ib.<sup>7,8</sup> For both, the rate determining step is the removal of a proton in base, while the incorporation of oxygen is fast. This reaction is quite different from the one involving fluorenes. The addition of m-trifluoromethylnitrobenzene has no effect of the rate of oxidation, and oxygen reacts more rapidly with the triphenylmethyl anion than with the corresponding radical. The actual mechanism of O<sub>2</sub> incorporation is not known since this is the fast step, and there is some belief<sup>10</sup> that the reaction is a solvent-cage type involving an electron transfer such as Scheme III.<sup>8,9</sup> Russell and coworkers,

#### Scheme III



however, propose<sup>8,9</sup> that this reaction may also involve radical intermediates, and may

proceed by a series of short chain steps such as in Scheme II. They note that the triphenylmethyl radical is more stable than the fluorenyl radical, and it should be able to escape from the solvent cage since the fluorenyl radical apparently does.

The tertiary hydroperoxides (or peroxy anions in base) are isolated if the solvent is hexamethylphosphoramide (HMPA), but in 80/20 DMSO/*tert*-butyl alcohol and base, the peroxy anion is reduced to the tertiary alcohol, while the DMSO is oxidized to the sulfone. In the actual chemiluminescence reactions in DMSO/base, the reduction of the peroxy anion is of little consequence. It is apparently not rapid enough to prevent some of this species from closing to the cyclic peroxide, although it could explain why quantum efficiencies are low compared to enzymatic oxidations. The above studies by Russell were not undertaken as a part of a study of chemiluminescence reactions, but they do seem to explain oxygen incorporation by anions in these chemiluminescent systems.

Some systems involve the removal of a proton from nitrogen instead of carbon. Chemiluminescence has been observed for certain indoles,<sup>11</sup> imidazoles,<sup>12</sup> and pyrroles.<sup>13</sup> The anion, produced in a solvent/base system, is oxidized to a radical, which can then form an adduct (on carbon) with oxygen. The mechanism is similar to the one shown in Scheme II.

The other system of oxygen incorporation involves the reaction with certain oxylate derivatives with hydrogen peroxide.<sup>14</sup> Under neutral or basic conditions in a solution of 1,2-dimethoxymethane, anhydrous H<sub>2</sub>O<sub>2</sub> reacts with an oxylate in a 1:1 stoichiometric ratio.<sup>15</sup> These monoperoxy acid species can then form one of several possible intermediates for chemiluminescence in the presence of a fluorescent compound. These reactions will be considered in detail later.

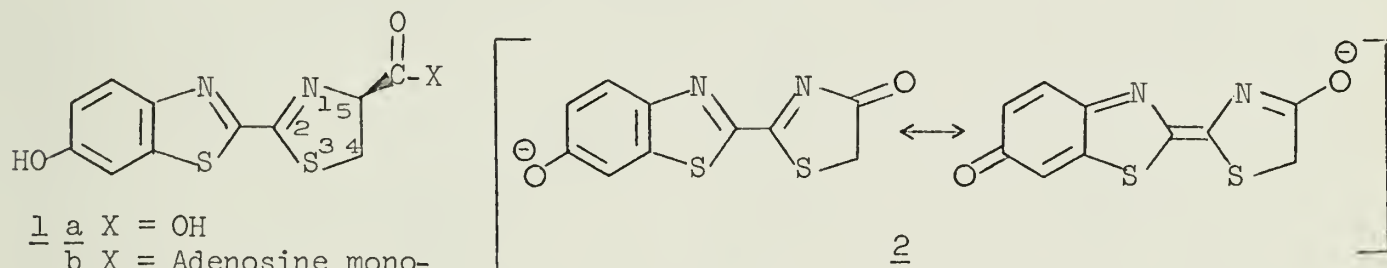
#### CHEMILUMINESCENCE OF BIOLUMINESCENT SYSTEMS

One of the most widely studied systems has been that of American firefly luciferin. A great deal of work has been done on the mechanism of its enzymatic

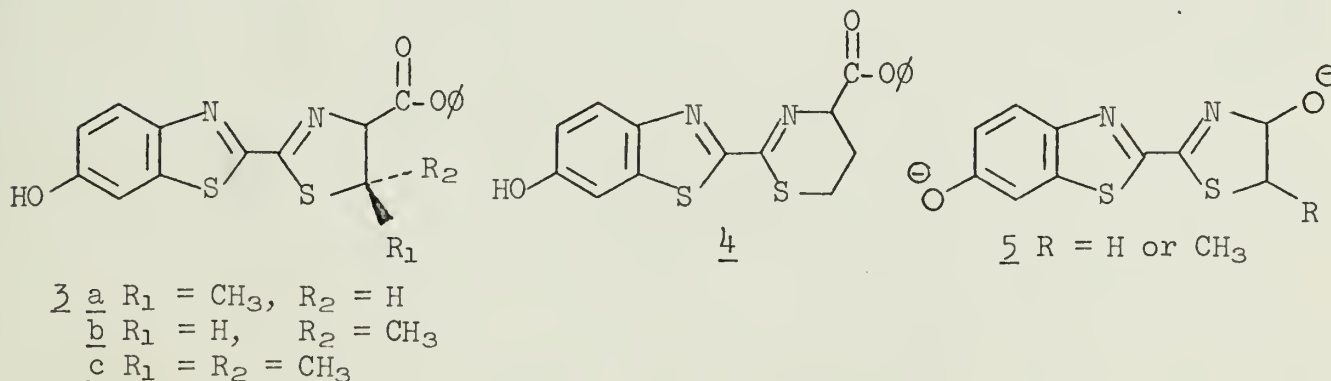
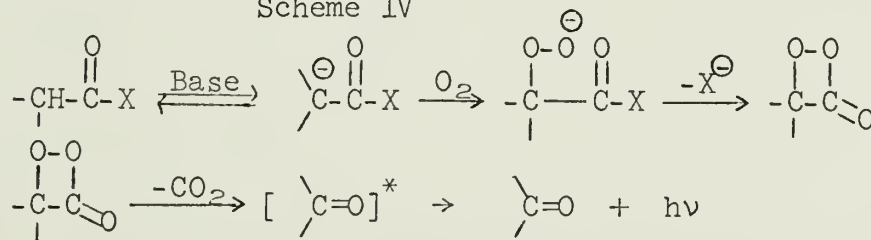


bioluminescence reaction,<sup>16</sup> and it was the first system of this type to be studied as a chemical problem. White and coworkers first deduced the structure of firefly luciferin<sup>17</sup> and proved the structure by complete synthesis.<sup>17,18</sup> The enzyme-catalyzed oxidation of the adenosine monophosphate (AMP) of the luciferin, 1b, exhibits a red emission (620 nm, quantum yield = 0.33) of light at an acidic pH, while at physiological pH, the normal yellow-green emission (565 nm, quantum yield = 0.88) is seen. Luciferins where X is the conjugate base of a strong acid (1b,c) show chemiluminescence in DMSO/*t*-BuO<sup>-</sup>.<sup>1</sup> McCapra and coworkers<sup>23</sup> suggested the mechanism in Scheme IV which involves the addition of O<sub>2</sub> to an anion to form the peroxy anion, which displaces X and forms a four-membered cyclic peroxide. This peroxide may then open to form two carbonyl groups, one of which is in an excited state and can return to the ground state by emitting light. This mechanism is applicable to any carboxylate derivative where the leaving group X is a weaker base than the peroxy anion and thus can be displaced by it.

Luciferin (1b,c) exhibits red chemiluminescence (630 nm) in DMSO and a small amount of *t*-BuO<sup>-</sup>. Hopkins and coworkers<sup>2</sup> proposed that the emitting species was the first excited singlet state of the mono-anion 2. They synthesized the carbonyl compound and showed that in DMSO/*t*-BuO<sup>-</sup> its fluorescence spectrum was identical to the chemiluminescence emission spectrum of the luciferin.<sup>1</sup> Upon addition of more base to the DMSO solution, the luciferin (1c) exhibits simultaneous red and green chemiluminescence, and in the presence of large amounts of base, there is a strong yellow-green emission (555 nm) similar to that observed in bioluminescence. In an attempt to explain the dependence of base concentration, White and coworkers<sup>19,20</sup> prepared compounds 3 a,b, and c and 4. Compounds 3 a,b show both chemiluminescent emissions just as the



Scheme IV

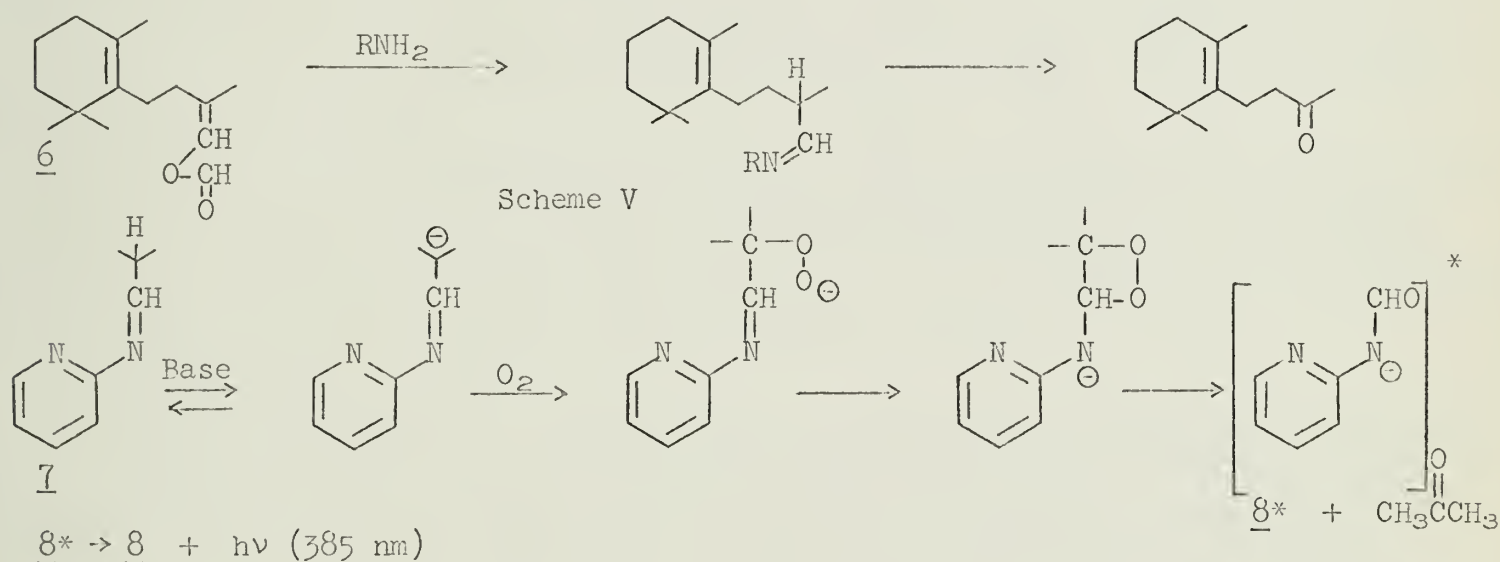


unsubstituted luciferin does, while 3 c and 4 show only the red emission. White,<sup>19,20</sup> suggests that the excited state of anion 2 is acidic,<sup>21,22</sup> and the excess base can



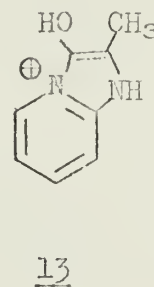
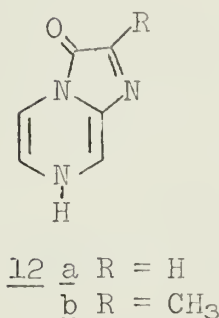
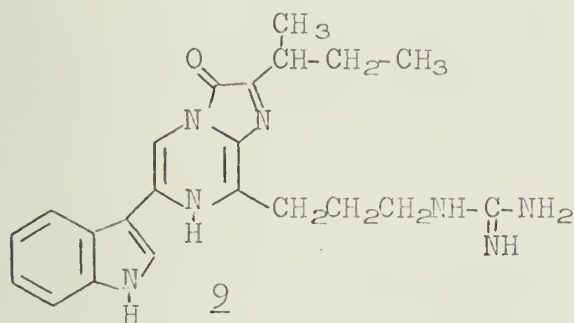
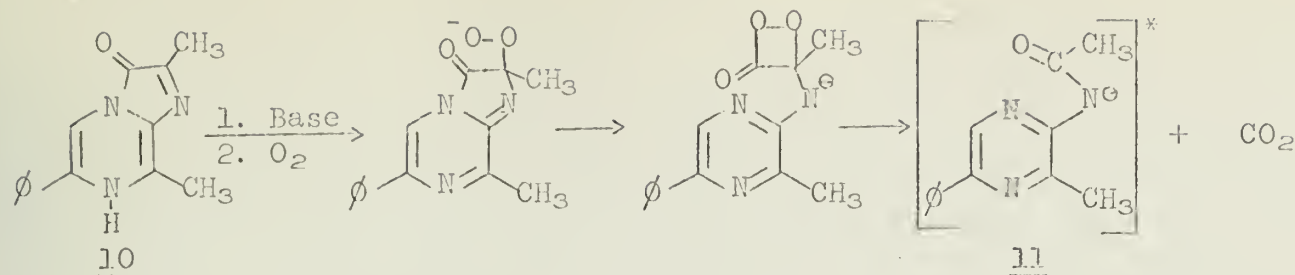
extract a proton from 1 b,c or 3 a,b before emission occurs, but this cannot happen in 3 c. In the case of 4, proton extraction is slower than emission due to the formation of a non-aromatic enolate. Thus White attributes the yellow-green chemiluminescence of 1 b,c and 3 a,b and the yellow-green fluorescence of their reaction mixtures to the first excited singlet state of the corresponding dianion 5. Species 5 is also thought to be responsible for the yellow-green bioluminescence where large amounts of base are not necessary since the removal of protons from carbons four and five proceeds enzymatically.

Another compound which exhibits bioluminescence is the luciferin from Latia neritoides, a fresh water limpet. Shimomura and Johnson<sup>24</sup> found that the most probable structure was that of compound 6. McCapra and Wrigglesworth<sup>25</sup> suggested that the bioluminescence could proceed by the oxidation of some suitable Schiff's base to a ketone and they noted that the formation of these Schiff's bases was common in enzyme chemistry. The Schiff's base could form by the reaction of the luciferin with an amine, RNH<sub>2</sub>, directly, or the reaction could first involve formation of the aldehyde. McCapra<sup>25</sup> used as a model the Schiff's base formed from 2-aminopyridine and isobutyraldehyde (7). The chemiluminescent oxidation of the model compound occurs in DMSO/t-BuO<sup>-</sup> and the light emitted is blue (385 nm). The workers isolated acetone and 2-formamidopyridine (8) from the reaction mixture, and they have proposed the mechanism in Scheme V for the reaction. The emitting species is the first excited state of the 2-formamidopyridine anion, since the fluorescence spectrum of that anion is identical to the chemiluminescence spectrum of the Schiff's base.



The bioluminescence of Cypridina hilgendorffii has long been known, and is one of the simplest of the bioluminescent systems, requiring only the luciferin, the luciferase, and molecular oxygen. The structure of the luciferin (9) was proposed by Kishi and coworkers,<sup>26</sup> who found that the complex molecule contained tryptamine, arginine, and L-isoleucine functionalities, which formed a dihydropyrazine structure, the oxidized species.<sup>23</sup> Chemiluminescent work has been done on simple compounds which are analogous to the oxidized part of the luciferin. McCapra and Chang<sup>27</sup> prepared compound 10, and they observed blue chemiluminescence (455 nm) when it was oxidized by air in DMSO/t-BuO<sup>-</sup>. The major product (89%) was the amide 11. The first excited singlet state of 11 is the emitting species, since its fluorescence spectrum is identical to the chemiluminescence spectrum. Chemiluminescence still occurs at 455 nm in a DMSO/triethylamine system, but the fluorescence of the amide in that medium occurs at 380 nm, which corresponds to the neutral amide, indicating that emission from the excited amide anion occurs prior to protonation. McCapra and Chang<sup>27</sup> propose the mechanism shown in Scheme VI.





The chemiluminescence of some other *Cypridina* analogs have also been studied in DMSO/base systems. T. Goto and coworkers<sup>28</sup> have used compounds **12** a, b, while McCapra and Wrigglesworth<sup>29</sup> have used compound **13**. These compounds all exhibit blue chemiluminescent emissions when oxidized in DMSO/base (**12** a, 450 nm; **12** b, 455 nm; **13**, 420 nm), and the products of the reactions are the corresponding amides. The proposed mechanisms correspond to the one given in Scheme VI. *Cypridina* luciferin itself also exhibits chemiluminescence in DMSO.

The luciferin from *Renillia reniformis* (sea pansy) produces a blue bioluminescence (485) nm) in a reaction catalyzed by an enzyme. Hori and Cormier<sup>30</sup> have done some work on the structure of this luciferin and they have indicated that the tentative structure is a substituted tryptamine (**14**) where R is fairly simple. The chemiluminescence of this luciferin may possibly be explained by the fact that it is a 3-substituted indole, and the chemiluminescence of these compounds is known.

#### OTHER CHEMILUMINESCENT SYSTEMS

Sugiyama and Akutagawa<sup>31</sup> have found that 2,3-dimethylindole (**15a**) and 2,3-dimethyl-3-indoyl peroxide (**16a**) emitted light (520 nm) when they were in a DMSO/KOH system with the dissolved oxygen present. They found that in the absence of O<sub>2</sub> **16a** emitted but **15a** did not. They also found that the main product of the chemiluminescent reactions of both compounds was the amide (**17a**). The fluorescence maximum of this compound in DMSO/base is at 520 nm, so the first excited singlet state of the amide anion is probably the emitting species. These workers proposed that **15a** was autoxidized to **16a** in the course of its chemiluminescence in DMSO/base. McCapra and Chang<sup>32</sup> investigated the chemiluminescence of indoyl peroxides **16a, b** and found that in DMSO/t-BuO<sup>-</sup> **16a** emitted at 518 nm and **16b** emitted at 495 nm. The major products (60-70%) of the chemiluminescence reactions are the anions of the amides **17a, b**. The fluorescence spectra of the anions are identical to the corresponding chemiluminescence spectra, indicating that they are the emitting species. McCapra and Chang<sup>32</sup> also found that the kinetics of the chemiluminescent reaction were first order in hydroperoxide (in the presence of excess base), and that when hydroperoxide **16b** was synthesized with <sup>18</sup>O<sub>2</sub> (16% enrichment), the amide **17b** was produced with total retention of the label in the amide carbonyl. The mechanism in Scheme VII fits the above data and has been proposed by several groups.<sup>4, 11, 32, 33</sup>

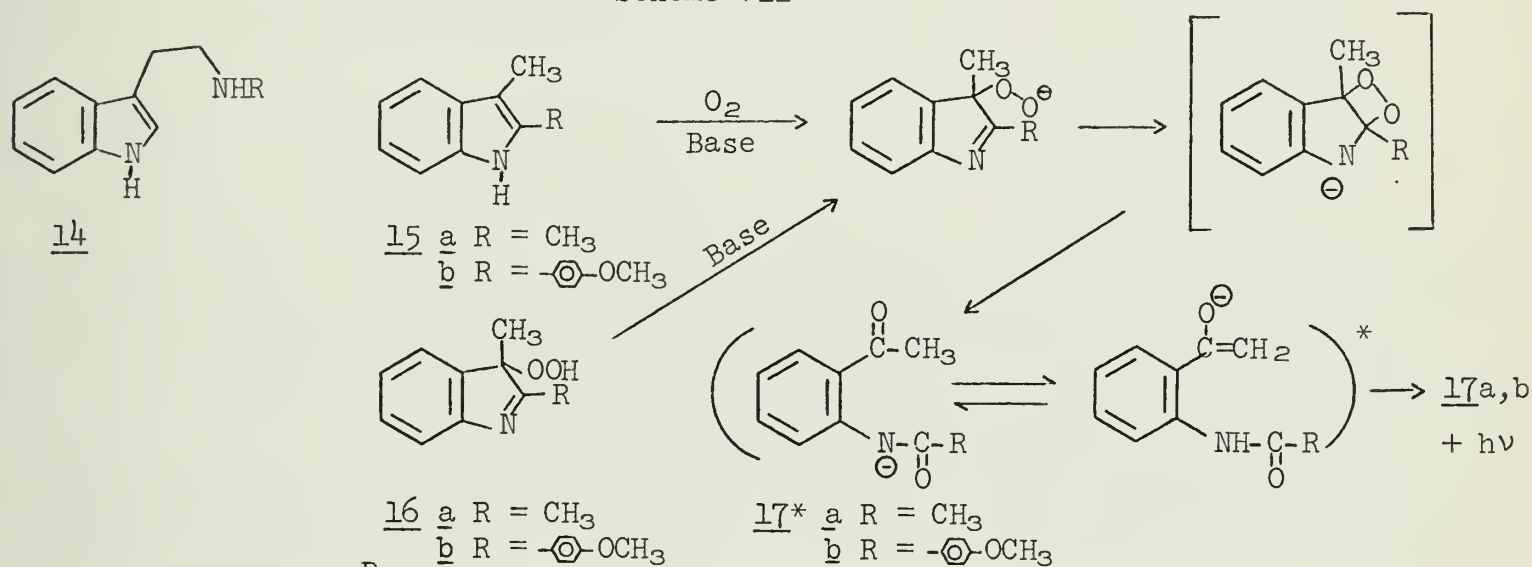
The first chemiluminescence reaction not based on analogies to biological systems was the oxidation of lophine, 2,4,5-triphenylimidazole (**18**) using strong base, oxygen, and some catalysts. The chemiluminescence (530 nm) occurs in ethanol/KOH (or DMSO/t-BuO<sup>-</sup>) containing molecular oxygen with or without oxidizing agents such as ethanolic



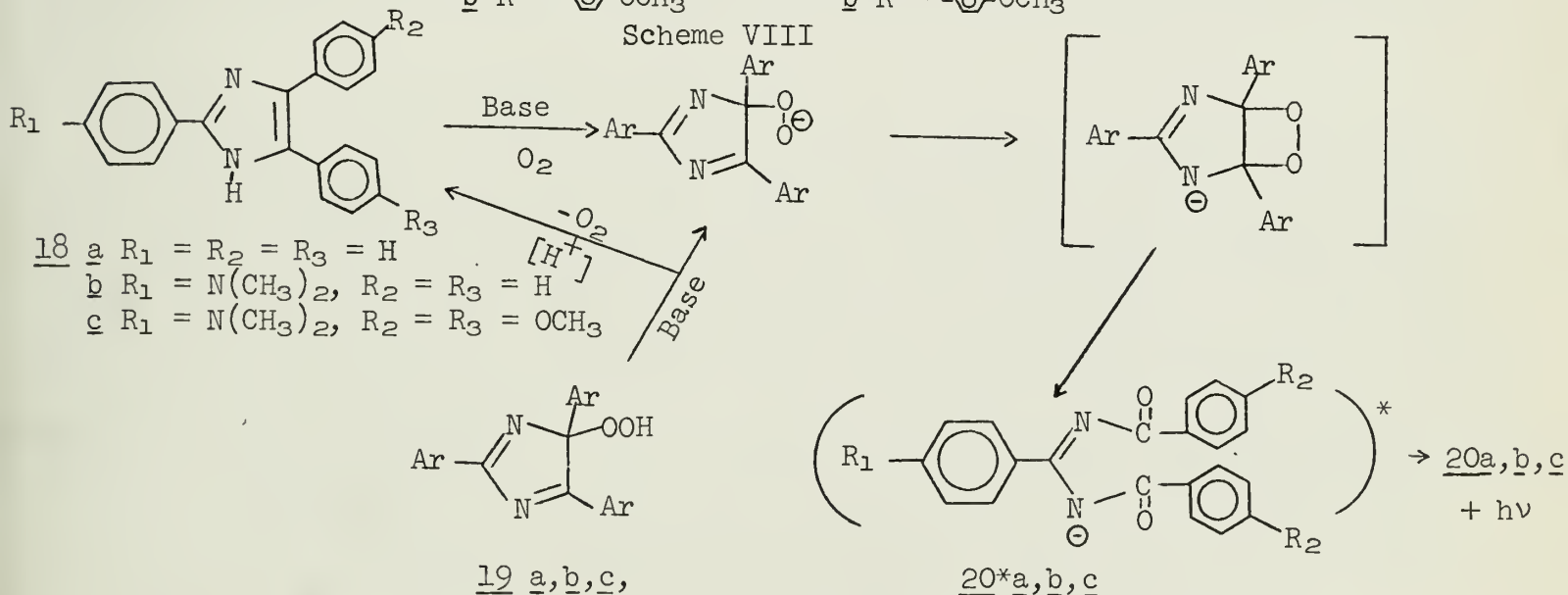
$\text{Br}_2$  or  $\text{K}_3\text{FeCN}_6$ ,<sup>12</sup> and it stops upon removal of dissolved oxygen. A purple intermediate associated with the chemiluminescence has been identified as the radical produced from oxidation of the anion.<sup>12</sup> Lophine hydroperoxide (19a) has been produced by reaction of the radical with oxygen or by photo-oxygenation ( $-70^\circ$ ) of lophine itself.<sup>34</sup> This peroxide also exhibits chemiluminescence upon treatment with base,<sup>5</sup> and its decomposition yields as major products lophine and the dibenzoylbenzamidine 20a. The lophine itself is not the emitter since the elimination of  $\text{O}_2$  probably would not provide sufficient energy for the 530 nm emission (about 53 Kcal). Evidence does not yet exist to show whether 20a is definitely the emitter for lophine.

Two groups<sup>5,12</sup> have proposed the mechanism in Scheme VIII for the lophine derivatives 18b,c. They proposed that the emitter in this case was definitely the corresponding benzamidine anion (20b,c) since their fluorescence spectra matched the chemiluminescence spectra (491 nm, 18b; 485 nm, 18c). Lophine itself (18a) is thus believed to proceed by this mechanism, but there is no definite evidence as yet to support this.

Scheme VII



Scheme VIII

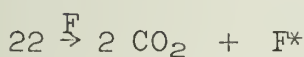
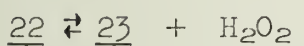
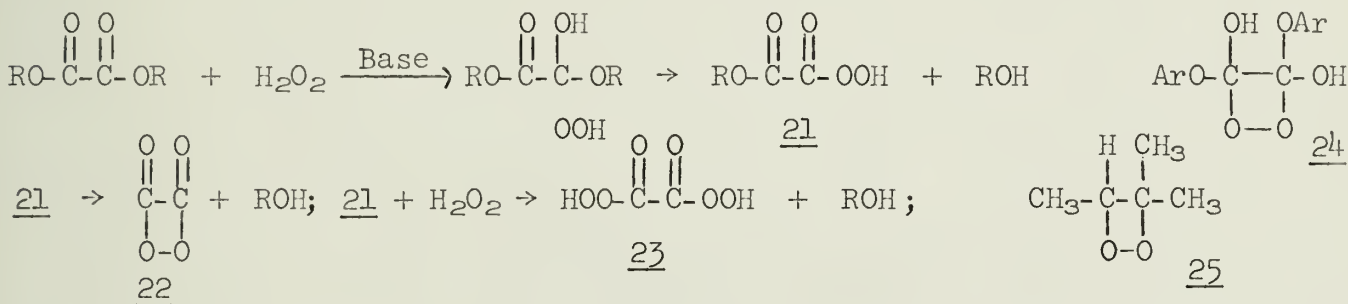


Rauhut and coworkers have done a great deal of work on the chemiluminescence of derivatives of oxalic acid.<sup>14,15,35,36</sup> In this type of chemiluminescence reaction, the oxalyl derivative is oxidized by  $\text{H}_2\text{O}_2$  and base in an ether-type solvent, and produces some excited species which does not show luminescence itself, but transfers its energy to a fluorescing compound (F) such as anthracene added to the reaction. Rauhut proposes the tentative mechanism in Scheme IX for electronegatively substituted aryl oxalates such as bis-(2,4-dinitrophenyl)-oxalate. The reaction also occurs with compounds such as oxalyl chloride,<sup>14</sup> pyridonyl glyoxals,<sup>37</sup> and phthalimido oxalates.<sup>38</sup> Since the  $\text{H}_2\text{O}_2$ /oxalate stoichiometry is 1:1, compound 23 is not an essential intermediate, although it may be involved at high peroxide concentration by providing 22. Decomposition



of 21 should give both CO<sub>2</sub> and CO, but only a trace of CO is detected.<sup>14</sup> Also, when the reaction is carried out with tert-butyl hydroperoxide or perbenzoic acid instead of H<sub>2</sub>O<sub>2</sub> the intermediates analogous to 21 provide only very weak chemiluminescence. When the reaction is run in the absence of a fluorescer, it does not exhibit luminescence, but a pad moistened with a solution of the fluorescer suspended above the reaction glows brightly. This indicates that a volatile intermediate is formed.<sup>14</sup> Rauhut and coworkers propose that 22 is the intermediate that fits the experimental data in this type of reaction. They also propose that 22 could form a charge transfer complex with the fluorescer, which upon decomposition could provide CO<sub>2</sub> and an excited fluorescer molecule (F\*) which would emit light and go to the ground state.<sup>14</sup> White and coworkers suggest that a compound such as 24 might be a more probably intermediate, even though it is not likely to be appreciably volatile.

Scheme IX



They also report that trimethyl-2-oxaoxetane (25), when decomposed thermally, leads to electronically excited states of acetone and/or acetaldehyde. These species can transfer their energy to anthracene (seen as fluorescence)<sup>41</sup> and to biacetyl (seen as phosphorescence).<sup>40</sup> They can also cause a "photochemical" reaction to occur, such

as the conversion of trans-stilbene to cis-stilbene.<sup>39</sup> This reaction and the others discussed in this seminar involve a common intermediate species, a cyclic four-membered peroxide whose thermal decomposition leaves a derived species in an excited state.

#### FORMATION OF ELECTRONICALLY EXCITED SPECIES

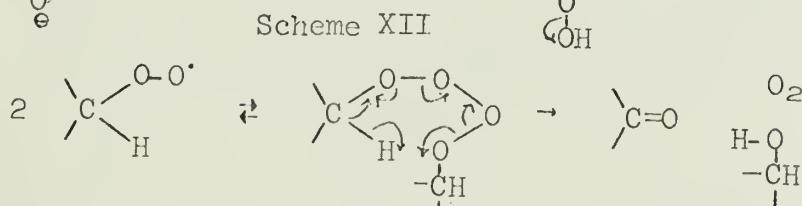
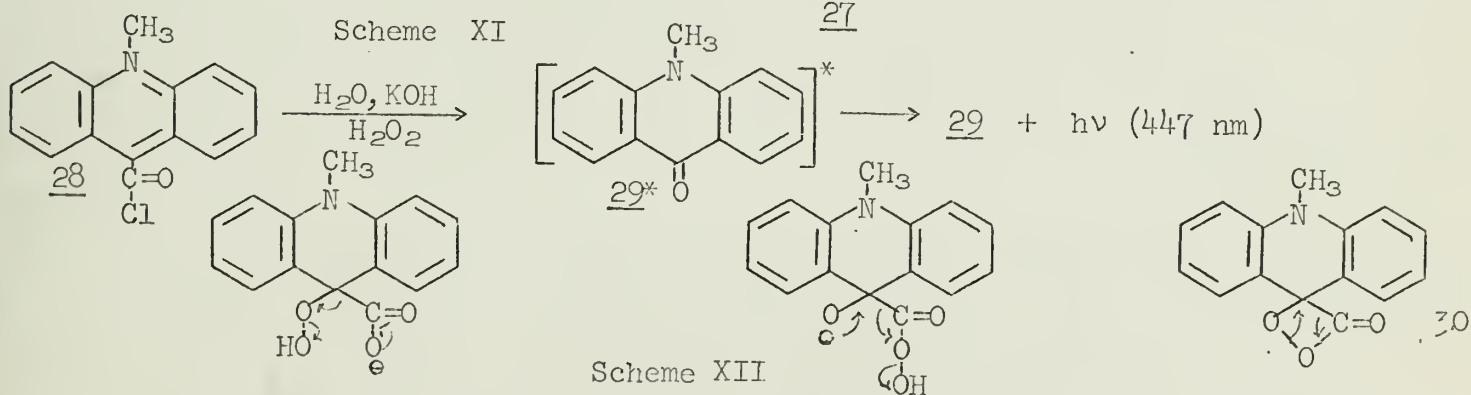
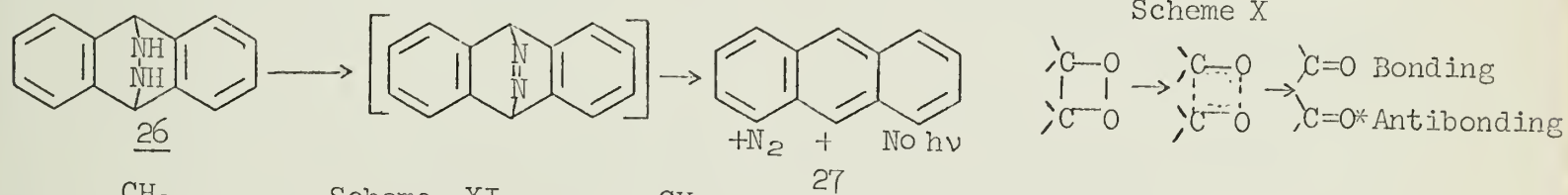
Since many chemiluminescent reactions involve oxygen or peroxides, and since ground state oxygen is in a triplet electronic state, early mechanistic proposals involved a vibrationally excited triplet. More recent studies have shown that almost invariably, chemiluminescent emissions take place from the excited singlet state of the molecule in question, and another approach has now been taken. A reaction with oxygen can lead to peroxides which can decompose to carbonyl groups. If these carbonyl functions are part of a fluorescent molecule, then peroxide decomposition could lead directly to an excited molecule.<sup>34</sup> This approach is especially good for a cyclic peroxide which could decompose to two carbonyl-containing species. The strain of the small ring and the stability of the carbonyl products indicates that this decomposition should be reasonably exothermic and should be able to provide enough energy for electronic excitation.<sup>41</sup> This energy must be equal to or less than the sum of the enthalpy of the reaction and the energy of activation. Thus the energy of excitation includes both the barrier to the excited state and the energy of the exothermic reaction, and there must be some mechanism to explain why some molecules can cross to an excited state and some cannot.<sup>31, 41, 42</sup> The exothermic reaction of 26 to fluorescent anthracene (27) is a "chemidarkness" reaction because it cannot yield excited 27.<sup>34</sup>

The decomposition of these cyclic peroxides is thought to be concerted. Rauhut<sup>14</sup> calculates that the production of excited singlet CO<sub>2</sub> from intermediate 22 alone would require an enthalpy increase of at least 110 Kcal., while the formation of two triplets would require at least as much. On the other hand concerted decomposition of 22 in the presence of a fluorescer (possibly as a charge-transfer complex) would require only 40 to 70 Kcal. enthalpy increase for excitation, and thus should be



avored. The concerted decomposition leads to two carbonyl groupings, and according to the Woodward-Hoffmann rules,<sup>46</sup> one of them must be formed in an excited state if the orbital symmetry of the process is conserved.<sup>41, 43, 44</sup> The fact that the reaction is quite exothermic probably explains the observation of the "forbidden" thermal process. The overall process is outlined in Scheme XI and the transition state is seen to contain 4n electrons, meaning that it is anti-aromatic and likely to involve electronic excitation.<sup>41, 43</sup> The energy in  $C=O^*$  can be redistributed over the entire fluorescent molecule which can then emit light and go to the ground state.<sup>41</sup>

The formation of an electronically excited molecule can be explained very well in the case of the concerted decomposition of cyclic peroxides but this is more difficult in the case of simple acyclic peroxide decomposition. Examples of this may be seen in early attempts to arrive at some type of mechanism for chemiluminescence observed in peroxide compounds. It was known that acridinium salts such as 28 exhibited chemiluminescence in  $H_2O_2/H_2O/KOH$ , and that the emitting species was the first excited singlet state of N-methyl acridone (29)<sup>45, 46</sup>. The acyclic intermediates shown account for formation of the N-methylacridone, but only the cyclic peroxide 30 can account for its formation in the excited state.<sup>45, 46</sup> The production of excited states has been noted for certain linear peroxides. Vassil'ev<sup>47, 48</sup> noted that the disproportionation of two secondary hydroperoxy radicals gave  $O_2$ , an alcohol, and ketone molecules in both the ground state and the first excited triplet state. He noted no excited singlet ketone molecules. Russell<sup>49</sup> proposed that the mechanism of that decomposition involved a cyclic transition state such as the one shown in Scheme XIII. Howard and Ingold<sup>50</sup> later defended this proposal and also reported that if the ketone was produced as a triplet, oxygen was eliminated in its ground triplet state. An alternate pair of products could be the ground state singlet ketone and excited singlet  $O_2$  ( $^1E_g^+$  or  $^1\Delta_g$ ). They also reported that tertiary hydroperoxy radicals disproportionated in a dark reaction to give ground state triplet oxygen and two tertiary alkoxy radicals. These reactions cannot explain the chemiluminescence of the systems previously discussed since they do not produce the excited singlet state species necessary for fluorescence, while the concerted decomposition of a four-membered cyclic peroxide can readily provide them.



## CONCLUSION

The formation of four-membered cyclic peroxides occurs in both biological and chemical systems and in a wide variety of compounds. They provide a route for the production of light by chemical energy, and while all are interesting reactions, some have been used to carry out reactions in a photochemical sense by providing electronic excitation without the need for an external light source.<sup>41, 51</sup>



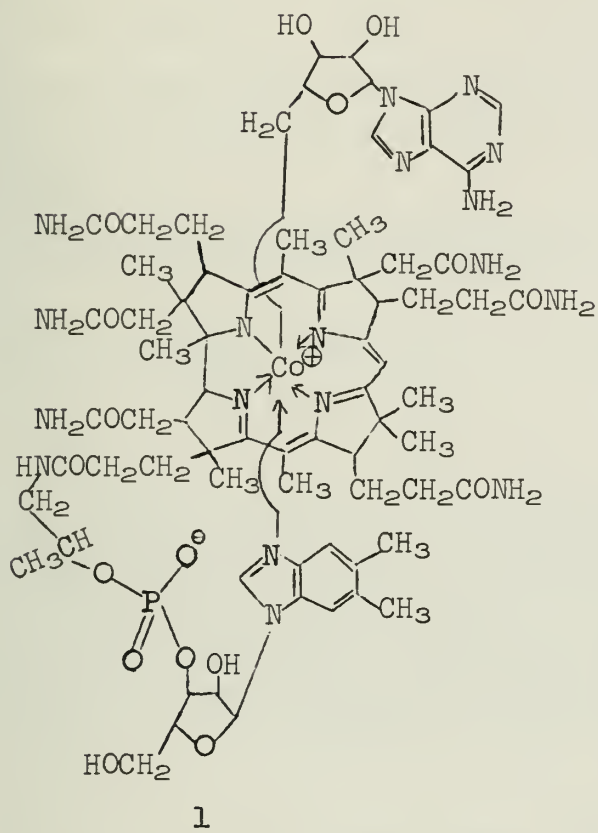
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## THE ORGANIC CHEMISTRY OF COBALOXIMES

Reported by John W. Williams

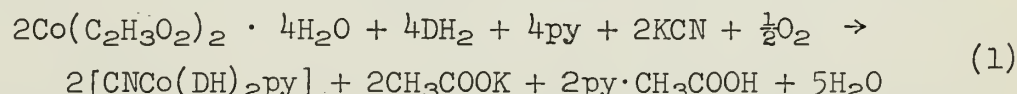
November 24, 1969



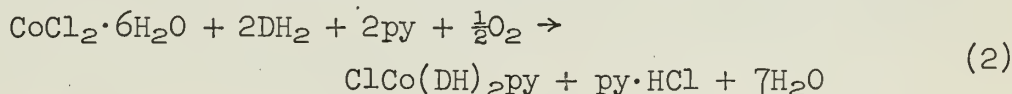
Interest in the chemistry of organocobalt compounds has rapidly increased since 1964, when it was first discovered<sup>1</sup> that the stable coenzyme of vitamin B<sub>12</sub> (1) contained a direct cobalt-carbon sigma bond between an adenosyl group and the central cobalt atom. Until 1964, the few compounds known to have Co-C bonds were quite unstable and highly reactive.<sup>2</sup>

The unusual chemistry of the cobalt atom in vitamin B<sub>12</sub> and its derivatives, the cobalamins, was at first thought to result from the electronic effects of the corrin ring system on the cobalt. However, it was soon discovered that the presence of the cobalt atom in any strong, essentially planar ligand field is all that is required for stability of the Co-C sigma bond. Therefore, a variety of ligands, such as bis(dimethylglyoxime), bis-(acetylacetonate) ethylenediimine, and bis(salicylaldehyde) ethylenediimine, have been used to prepare cobalamin model compounds.<sup>2</sup> The purpose of this seminar is to discuss the organic chemistry of the bis(dimethylglyoximate) cobalt complexes 2, named "cobaloximes," which were first reported<sup>3</sup> in 1964 to exhibit many of the same properties and reactions of the cobalamins.

The preparation of a cobaloxime, XCo(DH)<sub>2</sub>B (2: X = anion, e.g., CNO<sup>-</sup>, CN<sup>-</sup>, N<sub>3</sub><sup>-</sup>, SCN<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>; B = base, e.g., pyridine, tributylphosphine; DH = monoanion of dimethylglyoxime) can be carried out in a number of ways.<sup>4</sup> One method is via the Tschugaeff reaction between cobalt(II) acetate 4-hydrate, dimethylglyoxime, the alkali salt of the anion, and the base with the stoichiometry as shown in equation (1). When the

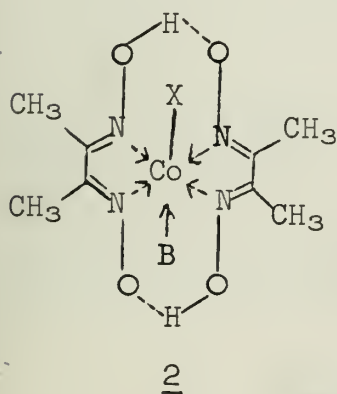
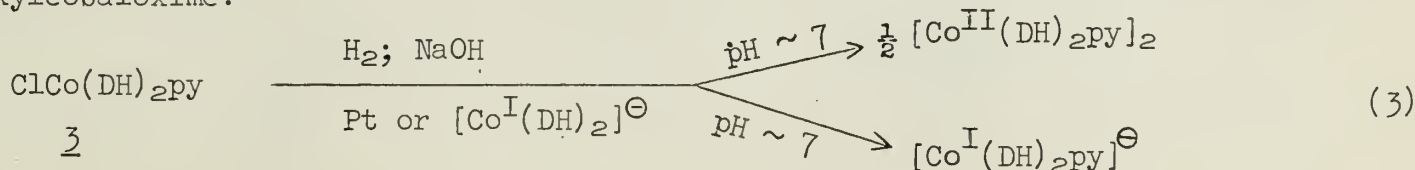


anion is chloride, CoCl<sub>2</sub>·6H<sub>2</sub>O is used as in equation (2) to obtain chloro(pyridine)cobaloxime(III) (3). Hydrogenation of

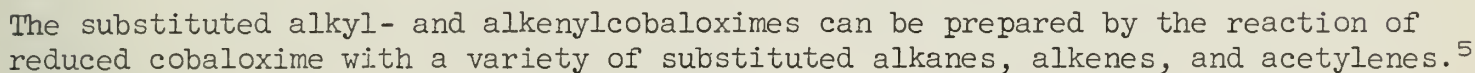
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3 as in equation (3), leads to a reduced cobaloxime, either cobaloxime (II) or cobaloxime (I), depending on the pH of the

solution. Reaction of 3 with an alkyl Grignard reagent yields the corresponding alkylcobaloxime.



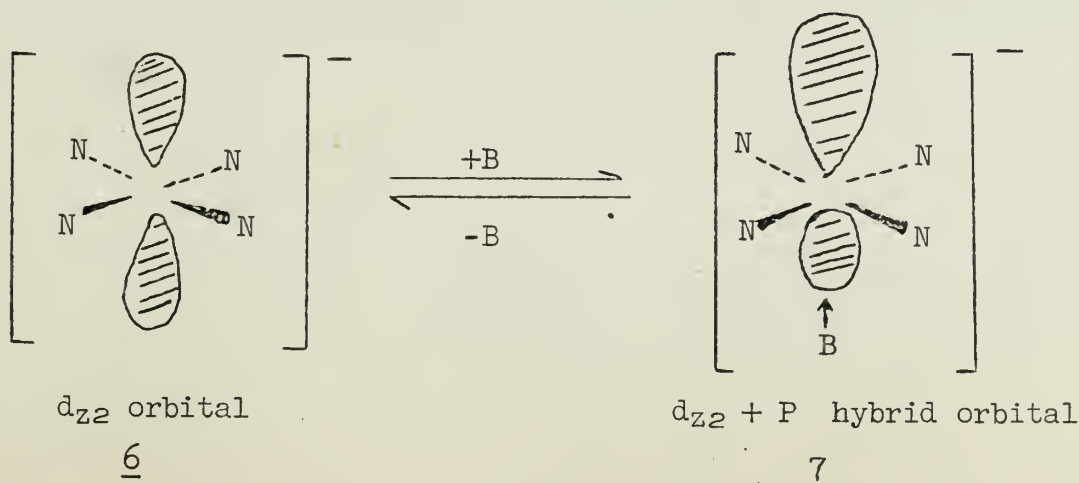
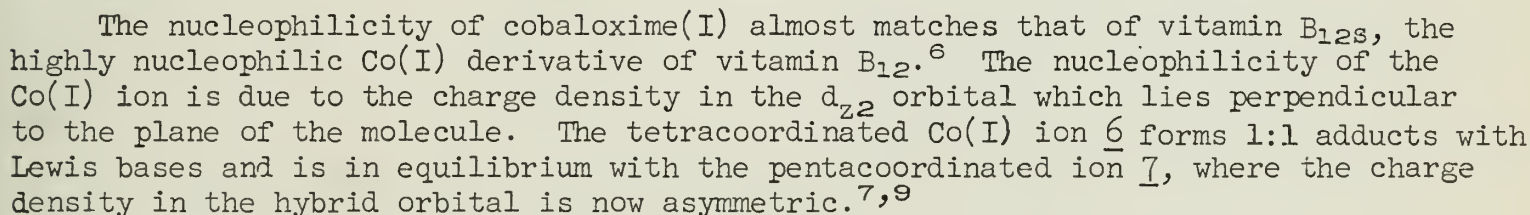
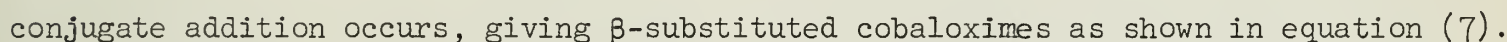




Cobaloxime(I) exists predominately as the spin-paired  $d^8$  ion 4 in alkaline or nearly neutral solutions according to the equilibrium shown in equation (5). The cobalt hydride 5, is unstable and exists in equilibrium with molecular hydrogen and cobaloxime (II).<sup>2,6</sup>

$$[\text{Co}^{\text{I}}(\text{DH})_2]^\ominus \xrightleftharpoons[\text{OH}^\ominus]{\text{H}_2\text{O}} [\text{H}-\text{Co}^{\text{I}}(\text{DH})_2] \rightleftharpoons [\text{Co}^{\text{II}}(\text{DH})_2] + \frac{1}{2}\text{H}_2$$

but the chemical behavior of the Co(I) ion in a variety of chelates<sup>5-8</sup> suggests the existence of such an acid as a reaction intermediate. In the case of the cobaloximes, the pH dependence of the reaction with substituted alkenes can be explained by the equilibrium between the acid 5 and its conjugate base 4. Schrauzer and Windgassen<sup>5</sup> proposed that in neutral solution the dimeric cobaloxime(II) is reduced to the Co(I) acid, H-Co<sup>I</sup>(DH)<sub>2</sub>py, which then adds to the substituted olefin to give α-substituted cobaloximes, as illustrated in equation (6). In alkaline solution the nucleophilic



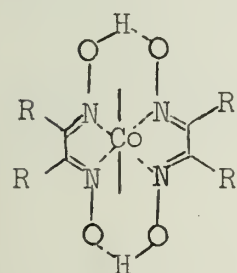


It can be seen by considering 7 that the nucleophilicity of the Co(I) ion might well be influenced by the effects of the axial bases and the planar ligands on the energy of the  $3d_{z^2}$  orbital and the charge density on the cobalt atom. Schrauzer and Deutsch<sup>9</sup> have compared the nucleophilicities of a number of cobalt chelates (Table I) and found that the effects of the ligands are mainly inductive ones. With the

Table I. Nucleophilic Reactivity Constants Toward Methyl Iodide<sup>a</sup>

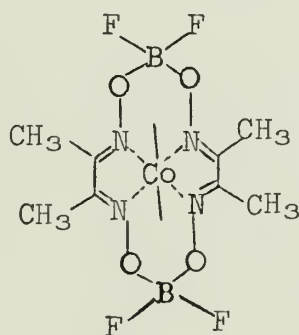
Nucleophile	$N_{CH_3I}^b$	Nucleophile	$N_{CH_3I}^b$
CH <sub>3</sub> OH	0.00	(n-C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> P	12.9
Co(CO) <sub>4</sub>	~ 3.50	<u>9</u> ·py	13.1
Cl <sup>-</sup>	4.37	<u>8</u> ·(n-C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> P	13.3
CN <sup>-</sup>	6.70	<u>8</u> ·(CH <sub>3</sub> ) <sub>2</sub> S	13.6
I <sup>-</sup>	9.92	<u>8</u> ·py	13.8 <sup>c</sup>
C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	~10.7	<u>8</u> (aquo)	14.3 <sup>c</sup>
<u>10</u> ·py	11.6	vitamin B <sub>12</sub> S	14.4

a) From refs. 6, 7, and 9; b) Using Pearson's<sup>10</sup> definition of  $N_{CH_3I} = \log(k_Y/k_{CH_3OH})$  where  $k_Y$  and  $k_{CH_3OH}$  are the second-order specific rate constants for attack by the nucleophile Y and by CH<sub>3</sub>OH, respectively, on CH<sub>3</sub>I at 25° in methanol as solvent; c) Calculated from relative rates of reaction with n-propyl chloride.



8, R = CH<sub>3</sub>;

9, R = C<sub>6</sub>H<sub>5</sub>



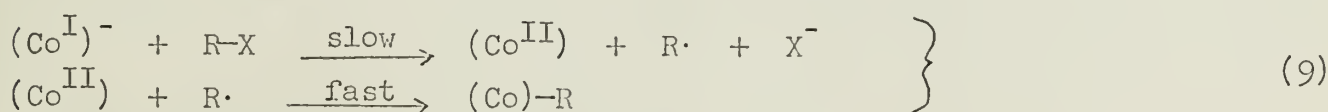
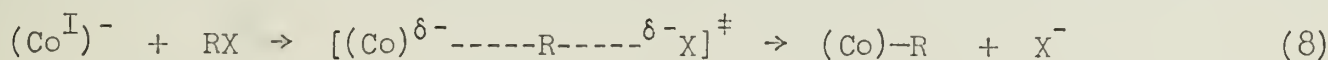
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cobaloximes 8 and 9, they found that 8 is the more nucleophilic, the inductive effect of the methyl groups enabling the dimethylglyoxime ligand to coordinate more strongly to the cobalt ion than can the diphenylglyoxime ligand. They also reported that the substitution of oxime hydrogens by BF<sub>2</sub>, as in 10, markedly decreases the nucleophilicity by reducing the electron density on the nitrogen atoms and the central cobalt atom.

Schrauzer and Deutsch<sup>9</sup> also compared the nucleophilicities of a number of base adducts of 8 (Table I), observing that the nucleophilicity of the Co(I) ion generally increases with increasing σ-donor ability and decreases with increasing π-acceptor ability of the coordinated axial base (e.g., substituting pyridine for tributylphosphine increases the nucleophilicity of 8).

Schrauzer and Deutsch<sup>9</sup> have reported that alkylation reactions of cobaloxime(I) follow a simple second-order rate law,  $-d[Co^I]/dt = k(RX)(Co^I)$ , which does not distinguish between an S<sub>N</sub>2 mechanism as in equation (8) and a free radical mechanism as in equation (9). After analyzing the kinetic data obtained from studies of the cobaloxime(I) reaction with alkyl halides in basic alcohol solutions, many similarities were observed between established S<sub>N</sub>2 displacements and the cobaloxime(I)<sup>N2</sup> displacements. Some of these similarities were in the sensitivity to leaving

group effects, sensitivity to structural features of the alkyl substrates, and sensitivity to substituent effects. By comparing the relative rates of a variety of cycloalkyl halide free-radical and S<sub>N</sub>2-type reactions, it was shown that the relative



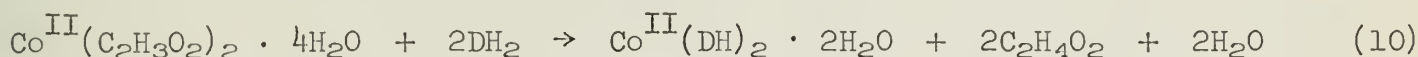
rates of cobaloxime(I) reactions with cycloalkyl bromides are indicative of a typical S<sub>N</sub>2 mechanism. The preliminary report of a large negative  $\Delta S^\ddagger$  (-20 to -30 eu) for the alkylation reactions, indicating increased order in the transition state, is attributed by Schrauzer to the change of the cobalt center, via an S<sub>N</sub>2 mechanism, from pentacoordinate in the reactant to hexacoordinate in the product. No large solvent dependence for the alkylation reactions of cobaloxime(I) was observed, this being consistent with an S<sub>N</sub>2 reaction between an ion and a neutral molecule.<sup>11</sup> All of these observations are in better agreement with the proposed classical S<sub>N</sub>2



mechanism in equation (8) than with the alternative mechanism shown in equation (9), which involves free-radical intermediates obtained by an electron-transfer process.

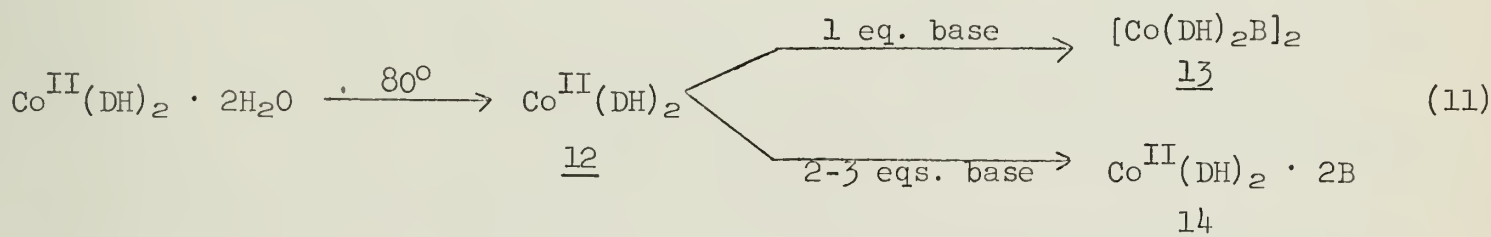
# COBALOXIME(II)

Diaquocobaloxime(II), 11, obtained by the reaction in equation (10) in the absence of air, is a low-spin  $d^7$  complex and is therefore paramagnetic. Dehydration



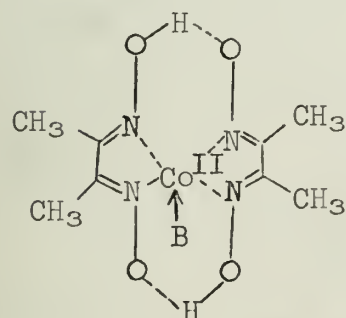
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of 11 in equation (11) yields the tetracoordinated solid 12, which is paramagnetic, air sensitive, and mildly hygroscopic.<sup>4</sup> The tetracoordinated complex 12 readily reacts with bases, such as pyridine or triphenylphosphine, to give either a 1:1 adduct when a stoichiometric amount of base is used or a 1:2 adduct when an excess of base is used.<sup>12</sup>



Schrauzer and Windgassen<sup>12</sup> reported in 1966 that magnetic susceptibility measurements on the solid 1:1 adduct indicated that it is diamagnetic and probably the solid dimer 13, containing a Co-Co bond. Schrauzer and Lee<sup>13</sup> have more recently reported that the 1:1 adduct does not show epr signals in the polycrystalline state, again indicating the diamagnetic dimer 13. When the solid dimer 13 is dissolved in aprotic solvents, epr signals are obtained indicating dissociation into the paramagnetic monomer 15.<sup>12,13</sup>

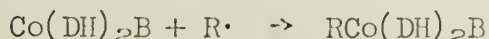
Schneider, Phelan, and Halpern<sup>14</sup> have recently obtained the 1:1 adduct as the monomer 15, both in the solid form and in benzene and acetone solutions. Both magnetic susceptibility measurements and epr spectra show the 1:1 adduct 15 to be paramagnetic, thus ruling out a dimeric structure such as 13. The 1:1 adducts were prepared according to Schrauzer's method and the chemical compositions are similar to those reported<sup>12</sup> earlier for the diamagnetic and presumably dimeric complexes. The possibility can not be excluded that Schrauzer's<sup>12</sup> 1:1 adducts may be different compounds from those most recently reported,<sup>14</sup> especially since in the preparation of the cobaloxime(II), the concentration of the solution probably determines whether the  $\text{Co}^{\text{II}}(\text{DH})_2\text{B}$  moiety crystallizes as the monomer or the dimer.<sup>15</sup>



15

The solid 1:2 base adduct 14 has been shown<sup>12-14</sup> to be paramagnetic by magnetic susceptibility measurements and epr spectra. The adduct 14 almost completely dissociates in solution into  $\text{Co}^{\text{II}}(\text{DH})_2\text{B}$  (15) and B, this being indicated by the fact that the epr spectra, visible-UV spectra, and the rates of reaction with benzyl bromide of 14 and 15 are essentially identical.<sup>14</sup>

The reactions of cobaloxime(II) with organic halides follow the second-order rate law,  $-d[\text{Co}^{\text{II}}]/dt = k[\text{Co}^{\text{II}}][\text{RX}]$ . Possible mechanisms for the reaction are the free-radical mechanism illustrated in equation (12) and a mechanism as shown in



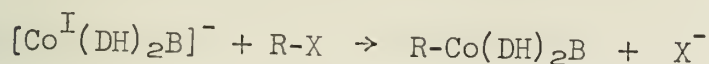
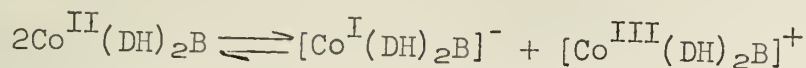
(12)

equation (13), which involves the disproportionation of cobaloxime(II) to cobaloxime(I) and cobaloxime(III), and then the  $\text{S}_{\text{N}}2$  reaction of cobaloxime(I) with the organic halide.<sup>14</sup> The latter mechanism has been reported<sup>9,16</sup> for alkylation

reactions in alkaline aqueous methanol solutions, where the disproportionation of



cobaloxime(II) is known to occur,<sup>2</sup> but such a mechanism is unlikely in benzene or acetone solutions, where cobaloxime(II) has been found to be quite stable.<sup>14</sup>



Kinetic measurements of the reaction of the monomer 15 with benzyl bromide, which showed, for instance, that the rate constant k increases by

about a factor of 5 in going from benzyl bromide to 1-bromoethylbenzene and that the effect on k of changing from benzene to acetone as solvent is relatively small, are best explained by the free-radical mechanism in equation (12). Also the observed second-order kinetics of the reaction probably rule out the mechanism in equation (13), since the disproportionation step, being either a preequilibrium or a rate-determining step, would require a higher than first-order dependence on the concentration of cobaloxime(II) (15).<sup>14</sup>

### COBALOXIMES(III)

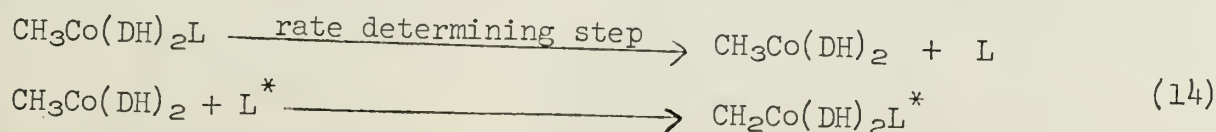
The most interesting members in the series of cobaloximes(III) are the alkylcobaloximes, 2 (X = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, etc.), their stable Co-C σ bond making them excellent models for the alkylcobalamins. The Co-C σ bond is formed by interaction of the 3d<sub>z<sup>2</sup></sub> orbital of the cobalt with the carbon and is essentially covalent. In the case of methylcobaloxime, 2 (X = CH<sub>3</sub>; B = pyridine), the methyl hydrogens do not undergo deuterium exchange and show neither acidic nor basic properties.<sup>2</sup> The alkylcobaloximes (in contrast to the organomagnesium halides) will not react with alkyl or aryl halides, CO<sub>2</sub>, and acyl halides. This demonstrates the unusual unreactivity of the Co-C bond in these organocobalt compounds.<sup>16</sup>

The Co<sup>III</sup> center in the alkylcobaloximes is viewed as being electrophilic, accepting charge via the σ bond from the alkyl group, evidenced by the reaction of cobaloxime(III) halides with Grignard reagents.<sup>17</sup> A correlation can be made<sup>18</sup> between the chemical shifts of the methyl hydrogens in the dimethylglyoxime ligands and the ability of the alkyl group to donate charge, since any change in electron density on the cobalt will affect the π-electron density of the planar ligand. The order observed is as would be expected, with the chemical shift of the methyl hydrogens shifting slightly to higher field (Δδ = 0.01-0.05) in the order: CH<sub>2</sub>CF<sub>3</sub> < CH<sub>3</sub> ≤ CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, M-C<sub>3</sub>H<sub>7</sub>.

The axial position in the cobaloximes is labilized to a degree depending on the σ-donor properties of the trans-ligand.<sup>17</sup> Studies of the effect of the trans-axial ligand on the chemical shifts of the α,β, and γ protons of pyridine in the XCo(DH)<sub>2</sub>py complexes<sup>18</sup> showed that the observed effects were opposite to those expected from changing the electron density at cobalt. The large low-field shift in the α-protons in changing from X = I (τ = 1.80) to X = CH<sub>3</sub> (τ = 1.37) might be due to a reduction in the anisotropic shielding by the cobalt atom or the π-electron system, such a reduction probably caused by an increase in the cobalt-pyridine bond length, since the chemical shifts of the pyridine protons in the alkylcobaloximes are close to the free pyridine values. The donation of charge by the alkyl group to the cobalt is also responsible for the observed slight shift to higher field of the pyridine protons with increasing σ-donor ability of the alkyl group.

Due to the trans-effect of the alkyl group on the other axial position, alkylcobaloximes will undergo ligand-exchange reactions, the axial base being readily displaced if the entering ligand has stronger donor-acceptor properties than the leaving ligand.<sup>16</sup>

Ludwick and Brown<sup>19</sup> concluded from kinetic studies of ligand exchanges in a series of CH<sub>3</sub>Co(DH)<sub>2</sub>L compounds that the cobalt center behaves as a "soft"<sup>20</sup> Lewis acid. In the exchange reaction shown in equation (14), dissociation is the



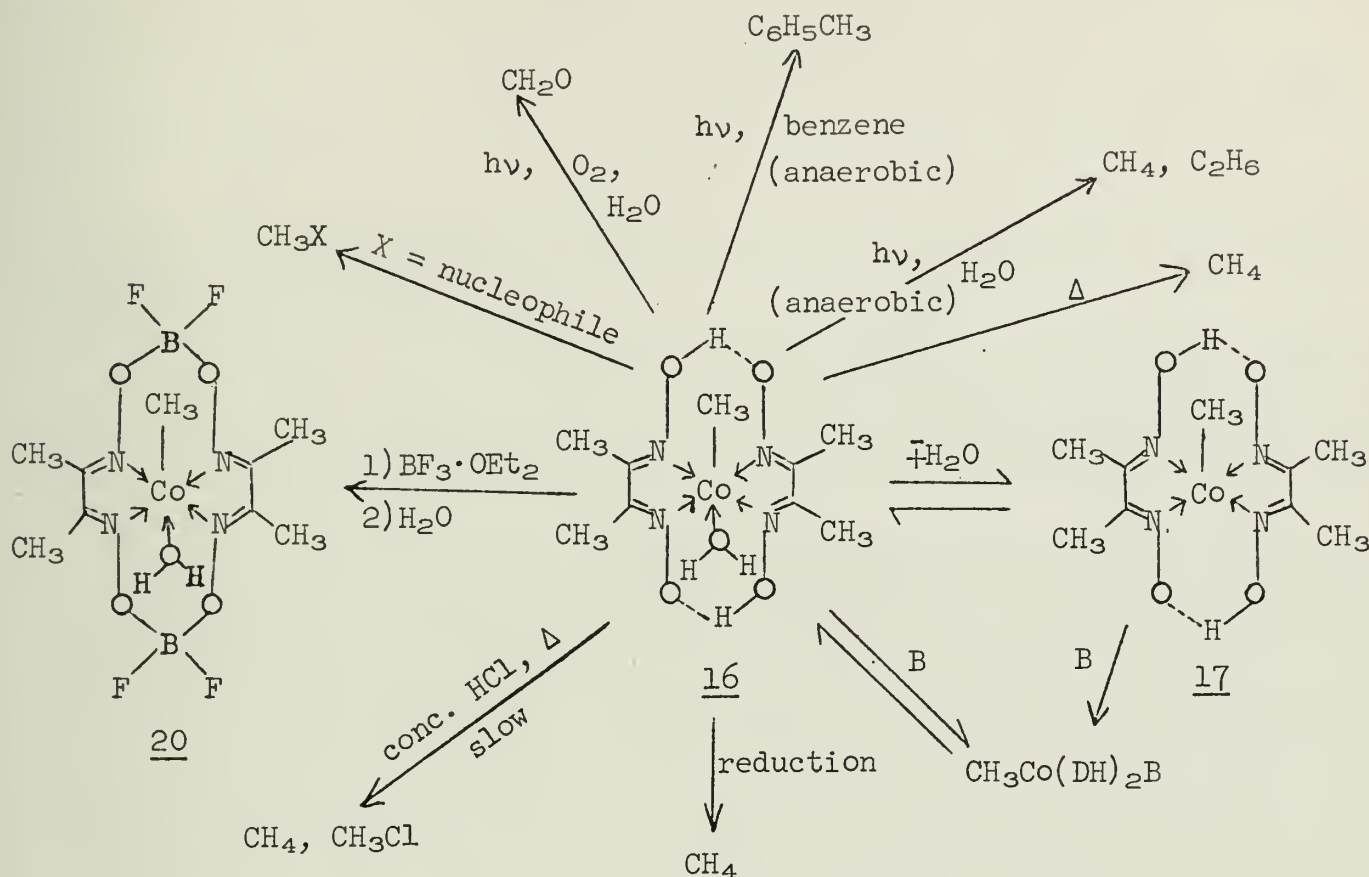
rate-determining process. The order of ligand exchange rates observed was: CH<sub>3</sub>CN, DMSO > (CH<sub>3</sub>)<sub>2</sub>S > S(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O (S-bonded) > (CH<sub>3</sub>)<sub>3</sub>N > P(OCH<sub>3</sub>)<sub>3</sub> > P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>, indicating a "soft" acid. Also indicating a "soft" acid is the fact that DMSO exhibits coordination isomerism with the CH<sub>3</sub>Co(DH)<sub>2</sub> moiety, low-temperature nmr spectra showing



absorptions for free, S-bonded, and O-bonded DMSO.

Some of the reactions of the alkyl cobaloximes are shown in Scheme I,<sup>2,16</sup> using methylaquocobaloxime, 16, as an example.

SCHEME I. Reactions of methylaquocobaloxime(III).

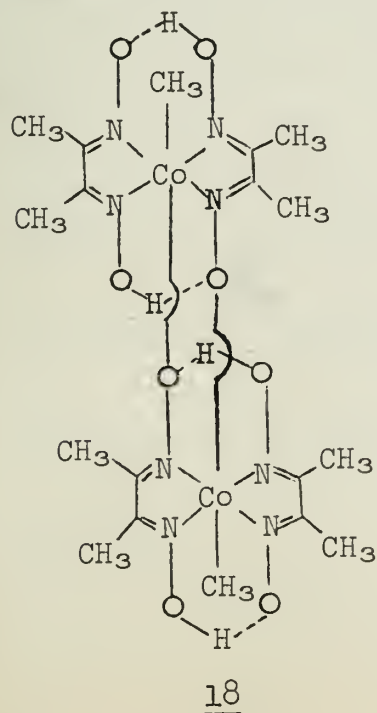


Methylaquocobaloxime (16) slowly yields methane and methylchloride in a 3:1 mixture when heated in concentrated HCl. It resists the action of cold concentrated  $\text{H}_2\text{SO}_4$  or KOH, but yields methane when heated with concentrated KOH. Dehydration of 16 in boiling benzene yields the corresponding anhydride,  $\text{CH}_3\text{Co}(\text{DH})_2$  (17) which may then react with a base, such as pyridine, to produce the adduct,  $\text{CH}_3\text{Co}(\text{DH})_2\text{B}$ .<sup>16</sup>

Since the dehydration of 16 did not result in Co-C bond cleavage, Schrauzer<sup>16</sup> concluded that the base components in the examples he studied were not essential for stabilization of the Co-C bonds. It was also proposed that the anhydrides,  $\text{RCo}(\text{DH})_2$ , may be associated in the solid state via interactions between the cobalt atoms and neighboring oxime oxygen anions. Ludwick and Brown<sup>19</sup> have recently proposed such an associated structure, 18, for dimeric  $\text{CH}_3\text{Co}(\text{DH})_2$ , nmr data being in accord with such a dimer formed via a Co-O linkage.

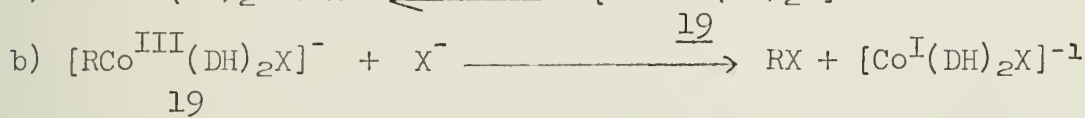
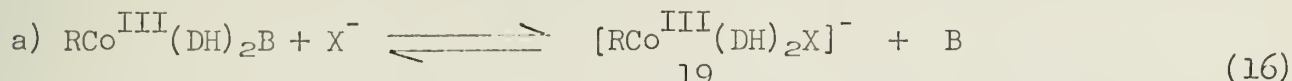
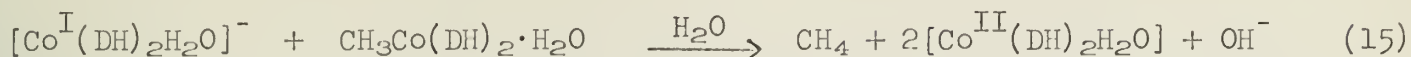
Reducing agents such as  $\text{NaBH}_4$  or  $\text{H}_2$  in the presence of a heavy metal catalyst will cleave  $\text{CH}_3\text{Co}(\text{DH})_2\text{H}_2\text{O}$  (16) yielding methane and cobaloxime(II). The action of cobaloxime(I) on 16 yields methane and cobaloxime(II), as shown in equation (15).<sup>16</sup>

The Co-C bond in the alkylcobaloximes is subject to cleavage by a number of nucleophiles, with attack occurring at the carbon. The cleavage reaction occurs via the mechanism shown in equation (16), where  $\text{X}$  = a nucleophile such as  $\text{HS}^-$ ,  $\text{RS}^-$ ,  $\text{CN}^-$ , or  $\text{R}_2\text{N}^-$  and  $\text{B}$  = a base such as pyridine. If a stoichiometric amount of the nucleophile is used, the cobaloxime(III) anion (19) is obtained, by displacement of the coordinated base. Therefore an excess of nucleophile is required





to obtain the slow cleavage reaction in equation (16b). Weaker nucleophiles such as  $\text{N}_3^-$  or  $\text{SCN}^-$  do not cleave the Co-C bond.<sup>16</sup> Also, the bond does not undergo CO or  $\text{CO}_2$  insertion reactions.<sup>2</sup>

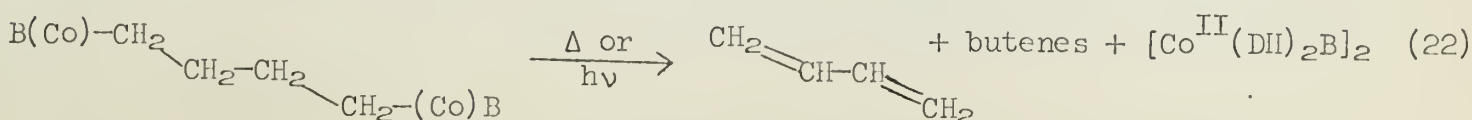
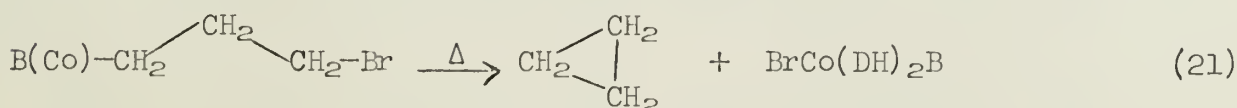
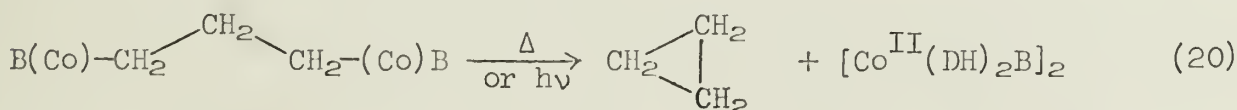
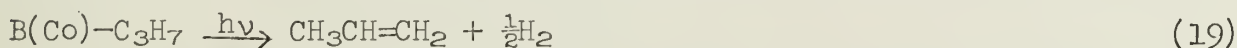
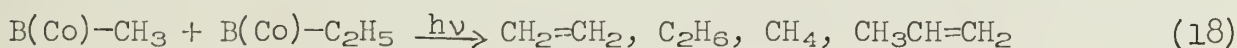
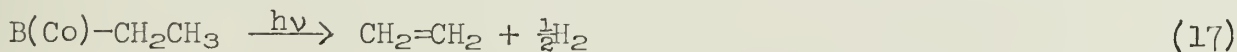


Schrauzer and Windgassen<sup>16</sup> have also reported the reaction of the alkylcobaloximes with boron trifluoride etherate to yield stable compounds such as 20, (Scheme I) containing O-BF<sub>2</sub>-O bridges.

The Co-C bond of the alkylcobaloximes may also be cleaved by photochemical and thermal reactions. Aerobic photolysis of  $\text{CH}_3\text{-Co}(\text{DH})_2\text{H}_2\text{O}$  (16) in  $\text{H}_2\text{O}$  yields mainly formaldehyde, while anaerobic photolysis of 16 in benzene yields toluene and in  $\text{H}_2\text{O}$  yields a mixture of methane and ethane. These results suggest that the initial step in the photolysis is homolytic cleavage of the Co-C bond to yield methyl radical and cobaloxime(II).<sup>16</sup>

The anaerobic photolysis of methylcobaloxime-d<sub>3</sub>, as well as of methylcobalamin-d<sub>3</sub>, has been reported by Schrauzer, Sibert, and Windgassen<sup>21</sup> to yield a product ethane whose composition has been shown by mass spectrography to be 89% C<sub>2</sub>D<sub>6</sub> and only 11% C<sub>2</sub>D<sub>3</sub>H<sub>3</sub>, the same results being obtained in both  $\text{H}_2\text{O}$  and  $\text{D}_2\text{O}$  as solvents. It was therefore concluded that ethane is formed in the anaerobic photolysis of 16 predominantly by dimerization of the methyl radical which is initially formed, rather than by "abstraction" of a methyl group from the ligands. The improbable "abstraction" mechanism was proposed by Hogenkamp in 1966<sup>22</sup> to explain the observed isotope dilution in the ethane formed by the anaerobic photolysis of <sup>14</sup>C-methylcobalamin; if the ethane were a product of radical dimerization, its specific activity would have been twice that of the starting material. Whether the ethane results from radical dimerization or from some other mechanism may well depend on the concentration of the Co complex in the photolysis solution.<sup>15</sup> Hogenkamp's<sup>22</sup> anaerobic photolyses of <sup>14</sup>C-methylcobalamin were carried out in quite dilute aqueous solution (3.31 μ moles/ml), whereas Schrauzer's deuterium studies<sup>21</sup> were carried out in solutions about eight or nine times more concentrated, making the radical dimerization reaction more favorable than in Hogenkamp's solutions.

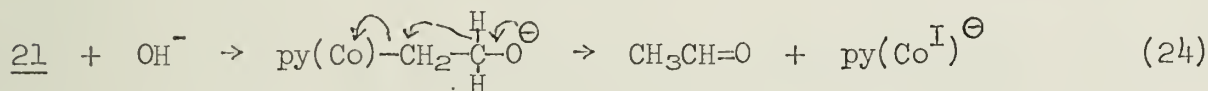
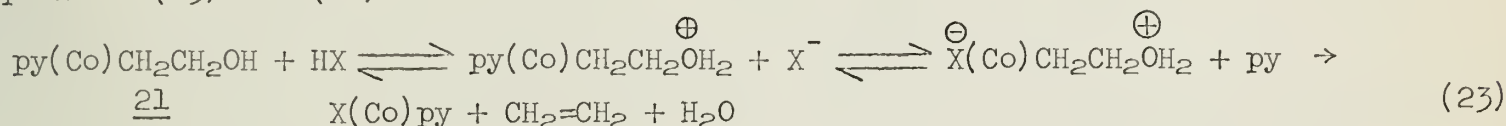
Schrauzer and co-workers<sup>2,16,21</sup> have also reported the anaerobic photolysis of other alkylcobaloximes. Photolysis of higher alkylcobaloximes yields predominantly alkenes, as shown in equations (17), (18), and (19), where the parentheses represent the dimethylglyoxime ligands and B = base. In equation (18), propane is produced by addition of a methyl radical to ethylene with subsequent loss of hydrogen.



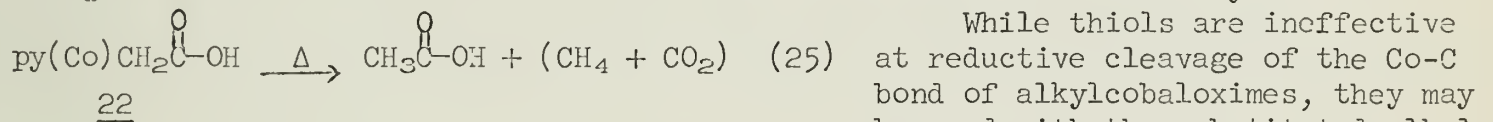


Thermal cleavage of methylcobaloxime yields mainly methane, while the higher alkylcobaloximes yield mainly olefins.<sup>21</sup> In equations (20) and (21), cyclopropane is produced by thermal cleavage of the Co-C bonds. The binuclear cobaloxime in equation (20), obtained by the reaction of cobaloxime(I) with 1,3-dibromopropane, also yields cyclopropane by photochemical cleavage of the Co-C bond. In equation (22), the preferred conformation of the binuclear cobaloxime is the strain-free transoid conformation of the tetramethylene bridge; therefore, instead of cyclobutane, 1,3-butadienes and butenes are formed.<sup>16</sup>

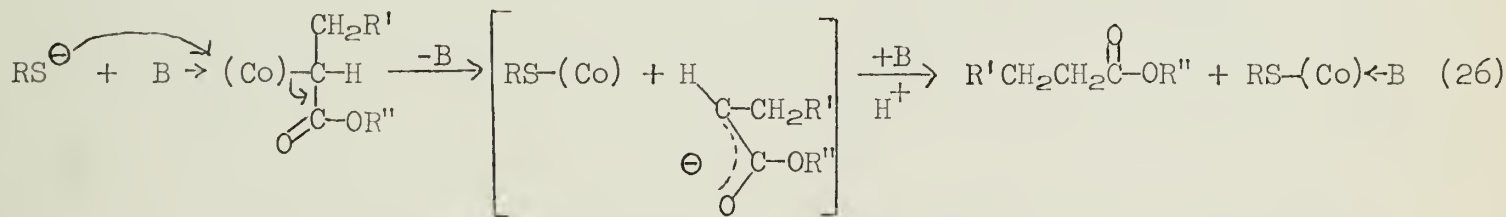
Introduction of substituents on the alkyl groups of the alkylcobaloximes causes a remarkable change in the reactivity of the Co-C bond. For example, ethylcobaloxime is stable toward acids or bases, but  $\beta$ -hydroxyethylcobaloxime (21) readily decomposes in either mildly acidic or basic media, as shown in the proposed mechanisms in equations (23) and (24).<sup>5</sup>



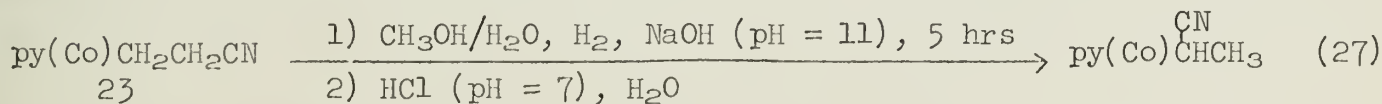
The cobaloxime carboxylic acids such as 22 are weaker acids than the free carboxylic acids, due to the proximity of the cobaloxime moiety. This "proximity effect" is better illustrated by the fact that  $\beta$ -carboxyethylcobaloxime ( $\text{pK}_a = 5.70$ ,  $25^\circ$ ; propionic acid,  $\text{pK}_a = 4.87$ ,  $25^\circ$ ) is a stronger acid than the  $\alpha$ -isomer ( $\text{pK}_a = 7.14$ ,  $25^\circ$ ). The thermal decomposition of carboxymethylcobaloxime (22) yields acetic acid and only small amounts of  $\text{CH}_4$  and  $\text{CO}_2$ , as shown in equation (25), indicating that bonding to the cobalt atom of the cobaloximes does not enhance decarboxylation.<sup>5</sup>



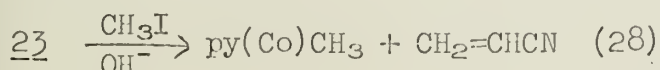
cobaloximes. Since  $\alpha$ -carboxylic (as well as  $\alpha$ -cyano) alkylcobaloximes are reduced more rapidly and quantitatively than the  $\beta$ -isomers, it is postulated that the  $\alpha$ -carbonyl group assists the reduction as in equation (26).<sup>5</sup>



$\beta$ -substituted ethylcobaloximes, such as 23, slowly rearrange to the  $\alpha$ -isomers under carefully controlled alkaline conditions as in equation (27). But with stronger



alkaline reagents, 23 undergoes elimination to the substituted olefin and cobaloxime(I). Also, in contrast to the alkylcobaloximes, the  $\beta$ -substituted alkylcobaloximes can undergo alkyl group exchange reactions, as shown in equation (28), due to the facile cleavage of the Co-C bond to form the nucleophilic cobaloxime(I), which then reacts with the alkylating reagent.<sup>5</sup>



Substituted allylcobaloximes, such as the one in equation (29), have the same sensitivity toward acids as the hydroxyethylcobaloxime 21. As equation (29) shows, the proposed mechanism again involves protonation and substitution.<sup>23</sup>





The cobaloximes are characterized by strong intramolecular hydrogen bonding in the dimethylglyoxime monoanion ligands. The infrared absorption band at  $1750\text{ cm}^{-1}$  is considered to indicate strong hydrogen bonding in the complex.<sup>24</sup> The measurement of the  $\text{pK}_a$ 's of cobaloximes such as  $[\text{BCo}(\text{DH})_2\text{B}]^n$  ( $n = -1, 0, +1$ ) show that the cobaloximes are generally weak acids, with  $\text{pK}_a$ 's ranging from 7.7 for  $\text{B} = \text{pyridine}$  to 12.6 for  $\text{B} = \text{CN}^-$ . The lower  $\text{pK}_a$ 's with bases such as pyridine are attributed to the  $\pi$ -acceptor capacity of the base, with this electronic effect being transmitted through the cobalt to the oximato group.<sup>25</sup>

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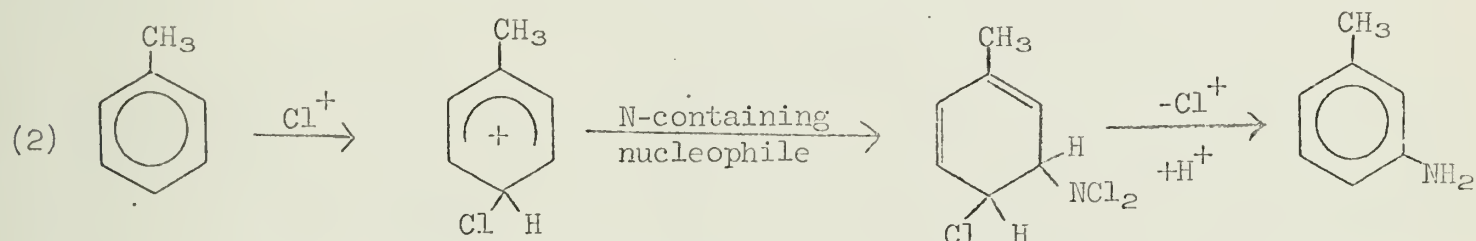
# N-HALAMINE AMINATION MECHANISMS

Reported by Charlotte A. Otto

December 4, 1969

Foot, in 1960,<sup>1</sup> observed that N-methyl-m-toluidine was the predominant basic product derived from treatment of toluene with N-chloromethylamine-aluminum chloride. To explain the unusual meta orientation in the presence of ortho-para directors, Peter Kovacic and co-workers have suggested an addition-elimination mechanism which they call "σ substitution."<sup>2</sup> It will be the purpose of this seminar to discuss the evidence for this mechanism.

A generalized reaction scheme includes the initial formation of a carbonium ion followed by attack of a nitrogen-containing nucleophile. A more specific reaction mechanism for aromatic systems (illustrated with toluene) has been proposed to explain the unusual meta orientation. This mechanism involves the initial formation of a σ complex (arenonium ion), followed by nucleophilic attack by a nitrogen-containing entity (perhaps  $\text{NCl}_2$ ), and finally rearomatization via elimination.



The first thorough study of the amination of toluene with trichloramine-aluminum chloride (1:2 molar ratio is usual) revealed products consisting of m-toluidine (42% yield, based on trichloramine), of 98% isomeric purity, and chlorotoluenes (ortho:meta:para = 31:1:68).<sup>2</sup> Amination of other monoalkylbenzenes lead to m-substituted anilines in yields ranging from 8% (m-t-butylaniline) to 53% (m-isopropylaniline) with most yields lying between 18 and 36%. An isomeric purity of >95% for distilled basic product was generally obtained.<sup>4</sup>

Amination of biphenyl yielded 3-aminobiphenyl (27% yield) as the only aromatic amine obtained.<sup>5</sup> Exclusive meta orientation with biphenyl is most unusual.

With this background, let us examine the proposed reaction mechanism. That a strong Lewis acid catalyst is needed for amination is demonstrated by several facts. First, no reaction occurs when the catalyst is excluded from the reaction mixture and second, the yield decreases as weaker Lewis acid catalysts are substituted, e.g., no reaction occurs with ferric chloride or stannic chloride as catalysts. A 3% yield is obtained with antimony (V) chloride.<sup>2</sup> The necessity of a Friedel-Crafts catalyst suggests a polar reaction mechanism.

The requirement of a twofold excess of aluminum chloride may be a result of complex formation between the catalyst and trichloramine and/or aniline product.<sup>2</sup> Another possibility is that product amine may be in the form  $\text{ArN}(\text{AlCl}_2)_2$ ; this form proposed by analogy with the proposed form of interaction between halamines and catalyst. Formation of  $\text{ArN}(\text{AlCl}_2)_2$ <sup>3</sup> could be written as:



The rate of this reaction, if it goes at all, must be extremely rapid, otherwise large amounts of nuclear chlorination of the amine would be obtained.<sup>6</sup> If this were the form of the amine at the end of the reaction, the free amine would be generated in workup procedures. Proof of the reaction would be difficult.

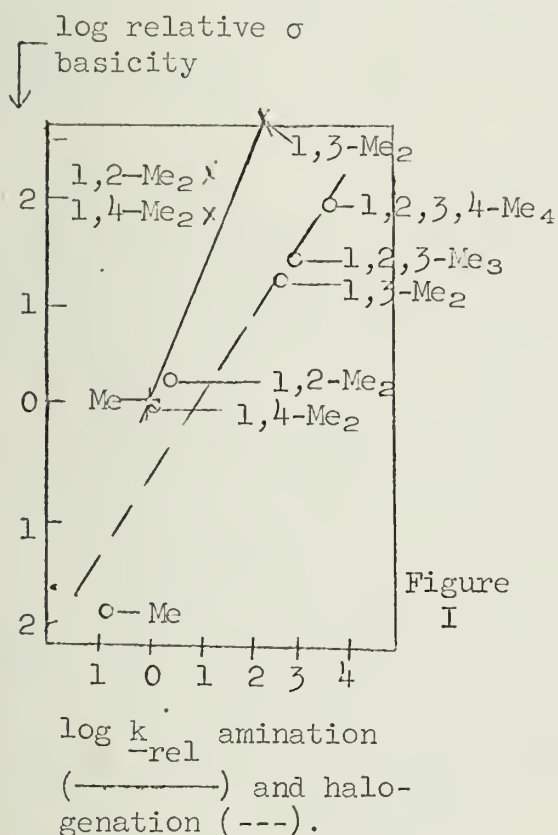
The first step proposed by Kovacic is a rate-determining formation of a σ complex. The existence of such complexes in mixtures of aromatics with strong Lewis acids has been well established.<sup>7</sup> The reaction yields reach a maximum at low temperatures<sup>2</sup> (for



the trichloramine reactions) where  $\sigma$  complexes might be expected to form and be stable.<sup>7</sup> Higher temperatures are sometimes necessary for other N-halamines.<sup>8</sup>

Plots of the logarithm of the relative rate ( $\log k_{rel}$ ) of amination of methylbenzenes versus  $\log k_{rel}$  for bromination with molecular bromine (slope = 1.4), and for chlorination with molecular chlorine (slope = 1.45) are linear. Aluminum bromide was used as catalyst for obtaining quantitative data as aluminum chloride reactions were too rapid.<sup>12</sup> The quantitative correspondence of  $\log k_{rel}$  for amination of methylbenzenes with  $\log k_{rel}$  for bromination, chlorination and protonation is compelling evidence for a rate-determining  $\sigma$  complex formation.

The relative basicities of methylbenzenes with respect to the formation of  $\sigma$  complexes (arenonium ions) ( $ArH_2^+ + BF_4^-$ ) have been determined.<sup>13</sup> Brown and Brady obtained a linear plot from the logarithm of the relative  $\sigma$  basicities of methylbenzenes versus  $\log k_{rel}$  for chlorination. They interpreted this to mean a crucial involvement of an arenonium ion.<sup>14</sup> When values of  $\log k_{rel}$  for amination of methylbenzenes are plotted against the values of their relative  $\sigma$  basicities, a linear relationship is obtained. (See Figure I). Kovacic interpreted this linearity to mean involvement of a  $\sigma$  complex as an intermediate and that similar energetics were involved.<sup>12</sup>



The presence of 3,5-diethylaniline from the amination of ethylbenzene and of 2,3,4-trimethylaniline in the products of mesitylene amination both support the postulated intermediacy of an arenonium ion. The neutral fraction of the mesitylene amination is (glpc analysis) a mixture indicative of gross rearrangement and disproportionation.<sup>4</sup>

There are two reasonable possibilities for the nature of the arenonium ion. The ion could arise from protonation yielding a protoarenonium ion or it could arise from attack by a chloronium ion yielding a chloroarenonium ion. That a protoarenonium ion is not likely is supported by the failure to observe an increase in yield of amine when water ( $H^+$ ) is added to the system toluene-trichloramine-aluminum chloride.<sup>2</sup> Likewise, no increase in yield was apparent with the addition of water to the *sec*-butylbenzene system.<sup>12</sup> Excess hydrogen chloride was added to the mixture of xylene and aluminum chloride to promote protoarenonium ion formation. Subsequent amination with trichloramine yielded 3,5-dimethylxylylidine in

76% yield. In the absence of hydrogen chloride, 97% of 3,5-dimethylxylylidine was obtained. The significant decrease in yield is attributed to substrate inactivation by protonation.<sup>15</sup>

The amount of protonation and rearrangement of *p*-cymene should be directly related as protonation is known to effect *p*-cymene rearrangement. Addition of water to the reaction mixture did not affect the yield of amination,<sup>16</sup> therefore a  $\sigma$  complex resulting from protonation does not seem likely.

The most convincing support for a chloroarenonium ion intermediate is evidence that N-chloroamines can halogenate aromatic systems.<sup>17-19</sup> Chloroaromatics are also the predominant products in the neutral fractions of amination reactions.

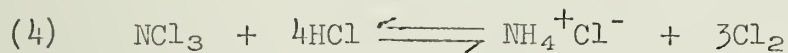
The next phase of the reaction is attack by a nitrogen-containing nucleophile. The nucleophile presumably could react with any of the Lewis acids present (aluminum chloride, hydrogen chloride or  $\sigma$  complex). Since amination is observed in fair yields, combination with the arenonium ion is favorable. Note that the usual path followed by  $\sigma$  complexes is the elimination of a proton to rearomatize the substrate, yielding overall *o*-,*p*-substitution.<sup>7</sup> While proton elimination probably occurs giving rise to



chloroaromatics, attack by a nucleophile is competitive, perhaps preferred with some substrates, with proton elimination.

The exact nature of the nucleophile is unknown at the present time, but some evidence exists which implicates  $\text{NCl}_2\text{H}$  or  $\text{NCl}_2^-$  as the attacking species. Kovacic argues that trichloramine is probably not the nucleophile by comparison with *t*-butylation data. When *o*-xylene is aminated, 57% of the basic product is 2,3-dimethylaniline (1,2,3 substitution) and 43% is 3,4-dimethylaniline (1,2,4 substitution).<sup>4</sup> When *o*-xylene is *t*-butylated, 100% 1,2,4 substitution is obtained.<sup>20</sup> If trichloramine were the aminating species, the steric factor would be slightly smaller than for a *t*-butyl group (a methyl group has slightly greater bulk than a chlorine atom).<sup>21</sup> The expected predominance of 1,2,4 substitution is not observed, therefore some other nitrogen-containing entity is the nucleophile. The validity of this argument is questionable as the transition states for both reactions are not expected to be equivalent as *t*-butylation is endothermic and trichloramine amination is exothermic. The longer carbon-nitrogen bond could permit accommodation of trichloramine.

The amination of *t*-butyl chloride with trichloramine-aluminum chloride, if quenched with ice water before all the trichloramine is added, yields 30% N,N-dichloro-*t*-butylamine.<sup>22</sup> This product suggests  $\text{NCl}_2\text{H}$  or  $\text{NCl}_2^-$  is the attacking species, according to Kovacic. Either of these could be generated in the reaction of trichloramine with hydrogen chloride to produce ammonium chloride and chlorine which probably proceeds in



a stepwise fashion.<sup>23</sup> Hydrogen chloride is produced by dehydrohalogenation of *t*-butyl chloride under the catalytic influence of aluminum chloride.<sup>22</sup> The formation of N,N-dichloro-*t*-butylamine is not conclusive evidence for participation of  $\text{NCl}_2\text{H}$  or  $\text{NCl}_2^-$ . One could envision attack of  $\text{Cl}^+$  or halamine on *t*-butylamine to yield the dichloroamine.

Ultraviolet spectral data from the amination of isopropylchloride provides support for a chlorine-containing nucleophile. In this amination isopropylchloride was added to a mixture of trichloramine-aluminum chloride. Iodometric titration immediately after addition indicated the presence of positive chlorine. The ultraviolet spectrum showed an initial  $\lambda_{\text{max}}$  at 320 nm which shifted with time to 312 nm and decreased in intensity. If positive chlorine was present as trichloramine, the  $\lambda_{\text{max}}$  should be at 345 nm. Chlorine absorbs at 335 nm; N,N-dichloroisopropylamine absorbs at 312 nm.<sup>22</sup> The initial  $\lambda_{\text{max}}$  (320 nm) is possibly due to three components (trichloramine, N,N-dichloroisopropylamine and chlorine) or to 2 components (N,N-dichloroisopropylamine and trichloramine or chlorine). The shift to 312 nm can be interpreted in terms of the formation of the dichloro compound with the decrease in peak intensity accompanying conversion into amine product. The spectral data can be interpreted as evidence for a chlorine-containing nucleophile. The data does not preclude a rapid formation of amine which is in equilibrium with dichloroamine. The peak intensity decrease could correspond to a shift in equilibrium as chlorine is swept out of the system.

One further piece of evidence is the formation of an N,N-dichloroadamantylamine as product in the amination of adamantane.<sup>24</sup> Presumably adamantane cannot generate olefinic material which would permit the conversion of the dichloro derivative to the amine via attack by hydrogen chloride generated in the system.

If the nucleophile does contain chlorine, one must explain the lack of extensive nuclear chlorination of the aromatic amines through intramolecular rearrangement as is expected.<sup>6</sup> The intermediate is expected to be highly unstable<sup>25</sup> and of transient existence. If such an intermediate is formed, it must undergo rapid transformation to some other intermediate ( $\text{ArN}(\text{AlCl}_2)_2$  for example), which does not contain nitrogen-chlorine bonds. The transformation must be more rapid than intramolecular chlorination. Possibly, a nucleophile other than  $\text{NCl}_2^-$  or  $\text{NCl}_2\text{H}$  ( $\text{NH}_2^-$  for example) is generated when an aromatic substrate is present. Conclusive data are lacking and the exact nature of the nucleophile remains unknown.

Before examining evidence for nucleophilic  $\sigma$  substitution which has been proposed to explain amination products of halobenzenes and which utilizes the same intermediate  $\sigma$  complex as  $\sigma$  substitution, other possible mechanisms for  $\sigma$  substitution should be reviewed.

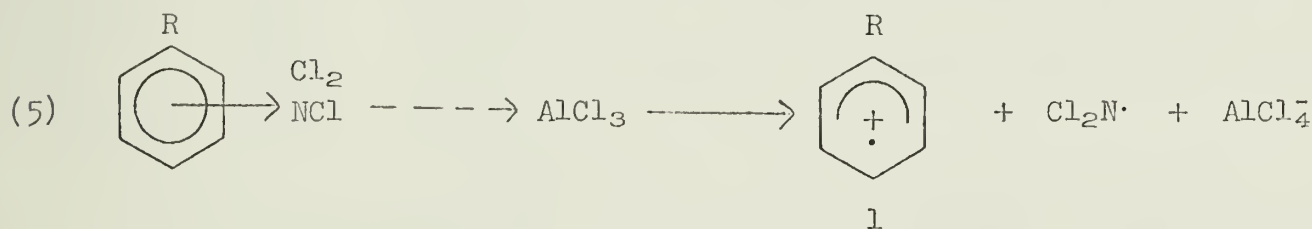


One possibility is an electrophilic substitution mechanism. This predicts ortho-para orientation of the incoming substituent when the compound contains a traditional o-, p-director (e.g., methyl or phenyl). Friedel-Crafts amination of aromatics with azides,<sup>26</sup> derivatives of hydroxylamines,<sup>26,27</sup> and hydrazoic acids<sup>26</sup> show ortho-para orientation and are generally considered to react via the electrophilic substitution mechanism. The exclusive meta orientation obtained from amination of biphenyl and the >98% isomeric purity of m-toluidine obtained from toluene amination are not easily explained by this mechanism.

Another reason for discounting electrophilic substitution is the amination results of mesitylene, which yielded only 2% of 2,4,6-trimethylaniline. Both p-xylene and mesitylene are resistant to t-butylation, however, p-xylene forms xylydines in reasonable yield so mesitylene amination should proceed. The poor yield could be explained by assuming an ortho or para proton is necessary for  $\sigma$  substitution. The small amount formed may be due to a high energy chloroarenonium ion, or to the incursion of electrophilic substitution to a slight extent.<sup>4</sup>

The various amine isomers that might be formed (e.g., o-, p- or m-toluidines) are stable under the reaction conditions<sup>2</sup> so an initial electrophilic attack with subsequent rearrangement is unlikely. Another intermediate postulated on the basis of  $\text{NCl}_2^-$  or  $\text{NCl}_2\text{H}$  as attacking species is, for toluene, N,N-dichloro-p-methylaniline. If formed, this compound may be highly susceptible to rearrangement. A driving force for rearrangement might be the lone pair of electrons on nitrogen, although other aminations with hydroxylamines, for example, which also contain nitrogen with a lone pair of electrons, do not undergo rearrangement. Therefore rearrangement of an  $-\text{NCl}_2$  function seems unlikely.<sup>12</sup>

A free radical might be generated as shown. Structure 1 might be energetically similar to a  $\sigma$  complex and possibly could go on to give products. One might also

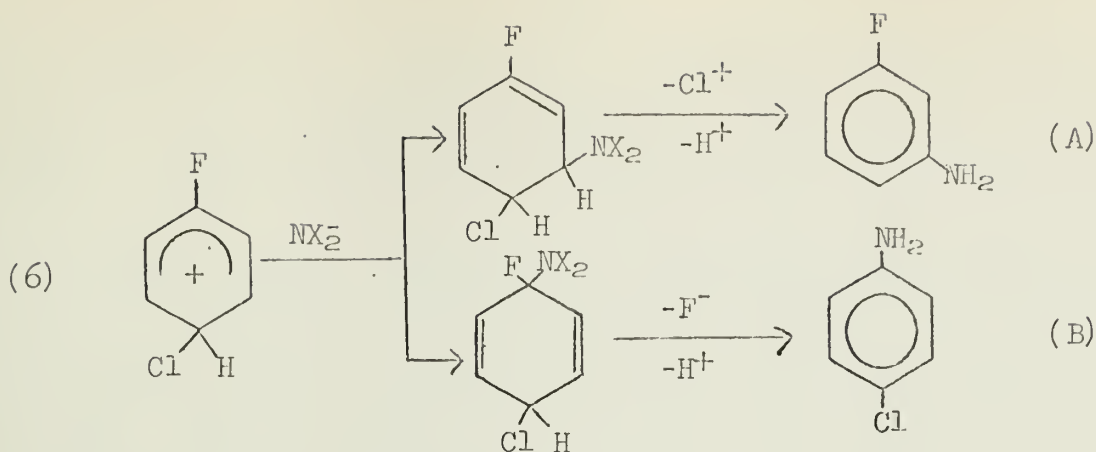


postulate the generation of  $\text{Cl}_2(\text{H})\text{N}^+$ . A free radical mechanism is ruled out on the basis of knowledge that radical substitution in toluene produces predominant ortho-para orientation. Amino radicals generated from N-chlorodimethylamine in concentrated sulfuric acid in the presence of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ,  $\text{TiCl}_3$  or  $\text{CuCl}$  attack toluene to give predominant ortho-para oriented products.<sup>28</sup> A nitrene intermediate arising from  $\sigma$  elimination is also eliminated from consideration as it is expected to react as a free radical.<sup>29</sup>

Direct nucleophilic substitution is discounted for several reasons. The low  $\sigma$  basicity of toluene precludes nucleophilic substitution except by extremely strong nucleophilic reagents. Classical nucleophilic substitution entails the displacement of a group (halide or alkoxyl, for example) attached to an aromatic nucleus which has been appropriately activated by a nitro or other electron-withdrawing substituent. In the amination of biphenyl and toluene, there are no activating groups present, and, in fact, the aromatic nucleus is deactivated for nucleophilic displacement.

Assuming the intermediacy of a chloroarenonium ion, one might ask what pathways such an intermediate could follow. Based on the results of amination of halobenzenes, in which m-haloanilines as well as o- and p-chloroanilines were found, Kovacic proposed two reaction pathways illustrated with fluorobenzene.<sup>3</sup> The relative rate of each pathway would determine the relative amount of the various products. Path A is the proposed  $\sigma$  substitution mechanism. Path B illustrates a nucleophilic addition at a carbon bearing a substituent (fluorine in the case shown) with a subsequent elimination of the substituent followed by proton loss (a concerted elimination of proton-substituent is possible). Path B mechanism is termed nucleophilic  $\sigma$  substitution by Kovacic.<sup>3</sup> Amination products of halobenzenes could arise from competition between paths A and B.





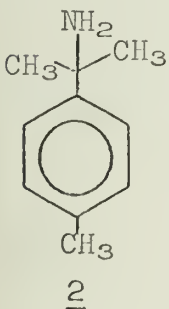
Evidence for path B is the decreasing ease of halogen replacement:  $F/Cl/Br = 40/15/7$ . The arrangement ( $F \gg Cl > Br$ ) is observed in the substitution of halogen by a methoxy group. The preferential site of nucleophilic attack is ortho or para to the halogen as predicted for nucleophilic substitution.<sup>3</sup>

The ratio of B to A could be affected by orientation of substituents, and by solvent and temperature changes. Meta isomers, elicited a higher ratio of B to A than did halobenzenes or o- or p-haloalkylbenzenes. (See Table I). The statistical probability of  $\sigma$  substitution is decreased by the presence of a meta substituent.

Substrate	B/A
m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> F	87/13
C <sub>6</sub> H <sub>5</sub> F	40/60
<u>o</u> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> F	36/64
<u>p</u> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> F	44/56
<u>m</u> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Cl	35/65
C <sub>6</sub> H <sub>5</sub> Cl	15/85
<u>o</u> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Cl	1/99
<u>p</u> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Cl	12/88

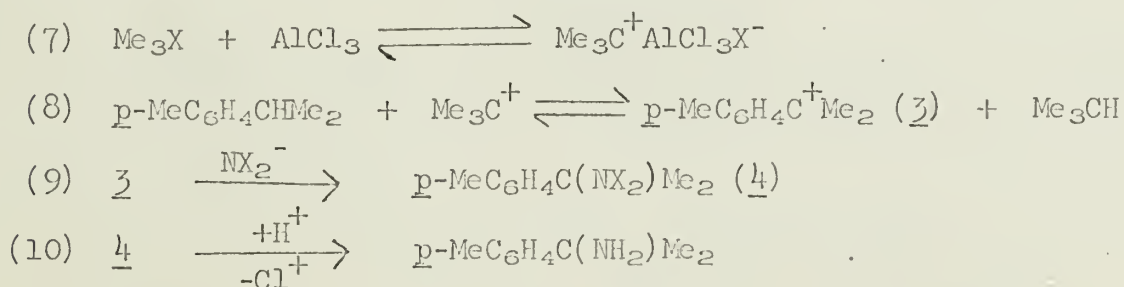
A solvent change from o-dichlorobenzene to 1,2-dichloroethane or a temperature change from 0 to 25° results in a reduction of the ratio with chloro- or bromobenzene, and an increase in the ratio with fluorobenzene.<sup>3</sup> The reason for the apparently inconsistent change in ratios is not known. The precise effect of changing solvent is unknown. A substantial increase in the ratio is observed when lithium chloride is added to the fluorobenzene-trichloramine-aluminum chloride mixture.<sup>3</sup> The salt may change the polarity of the medium or it may affect the nature of the catalyst.

Amination of p-cymene indicated that perhaps a  $\sigma$  complex was not required for an intermediate. The predominant product, 8-amino-p-cymene (2), was a result of side chain amination<sup>16</sup> and implied that existence of a cationic species was a more generalized requirement.



Side chain amination was postulated to proceed via abstraction of the isopropyl  $\alpha$ -hydrogen (in p-cymene) as a hydride ion. The resulting carbonium ion would then react with the nucleophile and eventually form the amine product. The hydride could be abstracted by the chloronium ion generated as before.<sup>16</sup> A similar role has been postulated for bromonium ion in the bromination of adamantane.<sup>30</sup>

In a subsequent study, Kovacic and co-workers found that the addition of t-butyl bromide to the p-cymene reaction mixture increased the yield of amine. The proposed reaction scheme is illustrated below where X = Cl or Br.<sup>31</sup>



The scheme supports the favorable influence of t-butyl halides, the necessity of a catalyst and the ability to proceed at low temperatures. That t-butyl bromide was more efficient than t-butyl chloride is explained by the more facile formation of t-butyl cation from the former. The yield of 2 passes through a maximum with increasing



amounts of t-butyl halide. A 10% yield of t-butylamine with large excesses of t-butyl halide was taken to mean that the t-butyl cation competed with 3 for the nucleophile.<sup>32</sup> That trichloramine-aluminum chloride reacts with t-butyl halides to form amines was supported by a study in which t-butyl halide was the only substrate present.<sup>22</sup>

The intermediacy of a carbonium ion is supported by the isolation of products derived from rearrangement. Amination of 3-(p-tolyl)pentane yielded 2-amino-2-(p-tolyl)pentane.<sup>32</sup> A relative rate study supplies evidence for a positively charged intermediate. The relative rate order observed with the series p-ZC<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)<sub>2</sub>, where Z = CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, and Cl, was 1.46-2.36:1.0:0.38 (for the order of Z given) (corrected statistically). This is qualitatively the same order observed for solvolysis of p-substituted cumyl chlorides in aqueous acetone at 0°, CH<sub>3</sub>:CH(CH<sub>3</sub>)<sub>2</sub>:Cl = 1.48:1.0:0.012.<sup>32</sup> The reaction media differ appreciably, so precise agreement is not expected.

Formation of isobutane supports the hydride transfer reaction (equation (8)). It has been well established that carbonium ions can function as hydride transfer agents.<sup>33</sup> The equilibrium of equation (8) should be related to the stability of the carbonium ions present. From solvolysis data, it is expected that the equilibrium would be displaced in favor of the t-benzylic cation as p-tolyl dimethylcarbinyl chloride undergoes solvolysis 26 times faster than phenyl dimethylcarbinyl chloride which undergoes an S<sub>N</sub><sup>1</sup> reaction 620 times faster than t-butyl chloride.<sup>31</sup>

Table II

Substrate	% yield
C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	36
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>3</sub>	31
C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	53
<u>p</u> -CH <sub>3</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	62
<u>p</u> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	80
<u>p</u> -(CH <sub>3</sub> ) <sub>2</sub> CHC <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	61

A study of Table II give further credence to the proposed t-benzylic cation intermediate. A t-benzylic cation is expected to be stabilized by p-alkyl groups, increased stabilization is reflected in the increase in yield of p-substituted aromatics. Halogens para to a t-benzylic cation have a similar resonance effect but an opposing inductive effect. The decreased reactivity expected is reflected in the increased temperatures needed for optimum results.<sup>32</sup>

Trichloramine-aluminum chloride amination of 1-methylcyclohexane to yield 82% 1-amino-1-methylcyclohexane<sup>34</sup> and amination of adamantane to yield 60% 1-aminoadamantane<sup>24</sup> gives credence to the generalized scheme of stable carbonium ion formation being a necessary prerequisite for amination to occur.

In conclusion, a general reaction mechanism can be summed up as follows. The catalyst, aluminum chloride combines with the trichloramine, or other chlorine-containing amine to generate a chloronium ion, or its equivalent, which either attacks an aromatic nucleus as a normal electrophile to form a  $\sigma$  complex, or abstracts hydride to form a carbonium ion. The positive species which is generated then undergoes nucleophilic attack (ortho or para to the  $\sigma$ -bonded chlorine) by a nitrogen-containing species. Subsequent loss of chloronium ion and addition of a proton produces the amine. If an aromatic substrate is used, the overall substitution is meta to an o-, p-directing substituent on the nucleus.

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## STRUCTURE STUDIES OF VIOMYCIN

Reported by Sharon Truitt

December 8, 1969

Viomycin is a tuberculostatic peptide antibiotic simultaneously isolated in 1951 in the soil screening programs of Chas. Pfizer<sup>1</sup> and Parke Davis & Co.<sup>2,3</sup> from two closely related strains, *Streptomyces puniceus* and *S. floridae*. Viomycin is especially effective against both streptomycin-sensitive and streptomycin-resistant strains of tubercle bacilli.<sup>1-5</sup> Since viomycin is generally less active and more toxic than streptomycin in the treatment of tuberculosis in humans,<sup>6</sup> it is one of the less important antibiotics in tuberculosis treatment.<sup>7</sup>

At least two other antibiotics are closely related to viomycin. Capreomycin<sup>8</sup> and tuberactinomycin<sup>9</sup> both have similar biological activity and degradation products. Unfortunately neither antibiotic's structure has as yet been fully elucidated.

This seminar will review the chemical and physical evidence used to propose partial structures of viomycin and structures of some of its degradation products, capreomycin, viomycin, dihydroviomycin, and viocidin acid, and the chromophore moiety. The trivial names established for the compounds will be used in this abstract.

## GENERAL PROPERTIES OF VIOMYCIN

Viomycin is a strongly basic polypeptide that is soluble in water and insoluble in most organic solvents.<sup>1</sup> It is isolated as its hydrochloride,<sup>2</sup> oxalate,<sup>1</sup> picrate,<sup>10</sup> and sulfate<sup>1</sup> salts. Its specific rotation is dependent upon its degree of hydration and the pH of the solution.<sup>2</sup> For hydrated viomycin sulfate,  $[\alpha]_D^{25}$  is  $-32^\circ$  (1 per cent, water),<sup>2</sup> and decomposition begins at  $280^\circ$ .<sup>1</sup> Several molecular formulas have been proposed, among them are  $C_{23}H_{36}N_{12}O_8$ ,<sup>10</sup>  $C_{23}H_{38}N_{12}O_9$ ,<sup>11</sup>  $C_{25}H_{43}N_{13}O_{10}$ .<sup>12</sup> Elemental analyses of the free bases<sup>13</sup> gave percentages that do not fit any of the proposed formulae sufficiently well to be conclusive. Several molecular weights, determined by molecular diffusion to be in the range 600-700, have been reported.<sup>14,15</sup> Mass spectral data have not been published.

The uv spectrum of viomycin contains only one strong absorption peak, which is at 268 nm,  $\epsilon$  24,600, at pH 1 and 290 nm,  $\epsilon$  16,000, at pH 10.<sup>10</sup> Its pK values of 8.2, 10.3, and  $> 12$  (in water) are attributed to two primary amino groups (Van Slyke determination) and a guanidine function.<sup>10</sup> The complete nmr of viomycin has not been published. Dyer and coworkers<sup>10</sup> did report, though, one proton at ca.  $\delta$  8 ppm ( $D_2O$ ).

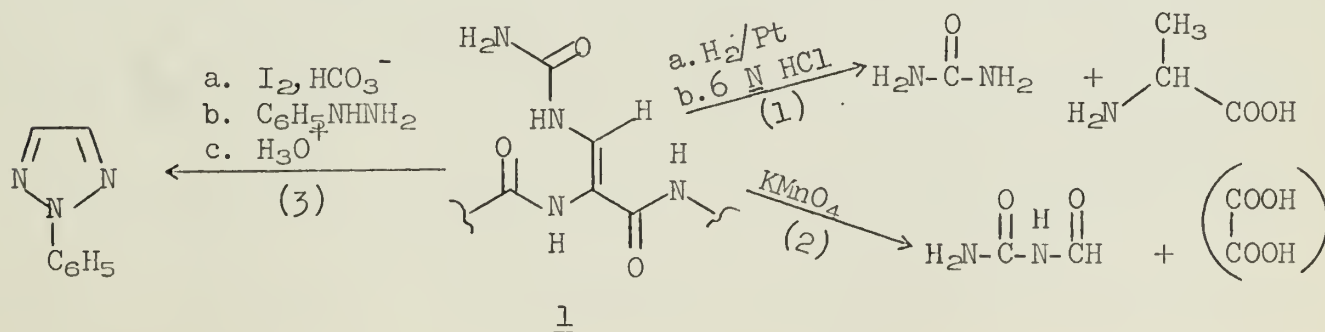
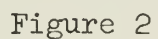
Qualitative tests. A large number of qualitative tests<sup>1,2,10,15,16</sup> have indicated the presence of a guanidino group, peptide bonds (indicative of the presence of amino acid residues), a urea and an easily oxidized group, possibly an aldehyde, and two primary amino groups.

Degradation products. Viomycin is relatively stable to acid but is hydrolyzed by mild alkali.<sup>2</sup> Complete acid hydrolysis produces L-serine, L- $\alpha,\beta$ -diaminopropionic acid, L- $\beta$ -lysine (3,6-diaminohexanoic acid),<sup>17</sup> and viomycin (in ratios 2:1:1:1), in addition to urea, carbon dioxide, ammonia, and traces of glycine.<sup>12,15,17</sup> The degradation is not entirely clean<sup>15</sup> for at least eight ninhydrin-positive spots have been observed on two-dimensional paper chromatography of the acid hydrolysate.<sup>16</sup> Mason<sup>15</sup> isolated three guanidino compounds, acidic, neutral, and basic in nature, under these conditions. Mild alkaline hydrolysis produces 2-aminopyrimidine, serine,  $\alpha,\beta$ -diaminopropionic acid,  $\beta$ -lysine, glycine, and urea.<sup>12,15,18</sup> Figure 1 summarizes these two degradations (reactions 1 and 2) as well as other reactions of viomycin. During hydrolysis  $\lambda_{max}$  268 nm disappears.

## STRUCTURE DETERMINATION OF THE CHROMOPHORE

Kinetic experiments by Mason<sup>15</sup> and Johnson and coworkers<sup>18</sup> demonstrated that in the hydrolysis of viomycin, the urea production rate was equal to the rate of loss of the chromophore. Since whenever urea is lost from the molecule the chromophore is lost, it remains intact only in reactions (4-a) and (6) of Fig. 1. Desureaviomycin,





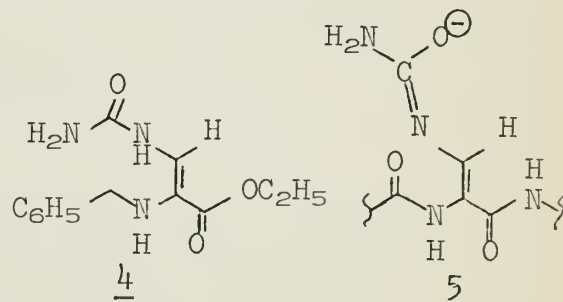


the degradation product formed upon hydrolytic loss of urea (0.1 N hydrochloric acid, 95°, 6 hr), does not absorb in the uv, <sup>10</sup> ( $\lambda_{\text{max}}$  272 nm after the addition of alkali<sup>18</sup>); thus, the guanidino group is not likely to be part of the chromophore.<sup>15,18</sup> (Kitagawa *et al.*<sup>33</sup> obtained desureaviomycin under identical conditions and reported  $\lambda_{\text{max}}$  272 nm,  $\epsilon$  8920 for it without its having been treated with base.) Chemical data supporting structure 1 as the chromophore moiety of viomycin is presented in Fig. 2.<sup>12\*</sup> Hydrogenation of viomycin (reaction 1)<sup>12</sup> produced urea and a perhydro derivative (cf. reaction (3), Fig. 1), and subsequent acid hydrolysis of the perhydro derivative produced L-serine, L- $\alpha,\beta$ -diaminopropionic acid, L- $\beta$ -lysine, capreomycinidine (from the guanidine moiety<sup>18</sup>), (2), and alanine (2:1:1:1:1). Since alanine is not derived from any of the amino acids in viomycin, it must be a reduction product of the chromophore.<sup>12</sup> The gross structure of capreomycinidine has been proved by total synthesis,<sup>19</sup> and its absolute and relative stereochemistry has been established by correlating its structure with that of closely-related viomycinidine (3),<sup>20</sup> whose structure has been determined by X-ray analyses.<sup>21-23</sup> Capreomycinidine, along with alanine, serine,  $\alpha,\beta$ -diaminopropionic acid,  $\beta$ -lysine, carbon dioxide, ammonia, and a ninhydrin-positive component, has been obtained upon acid hydrolysis of capreomycin.<sup>24</sup>

Permanganate oxidation of viomycin<sup>15,25</sup> at the ethyleneic linkage of the chromophore (reaction 2) produced formyl urea as well as the usual acid hydrolysis products of viomycin. There is disagreement between workers<sup>12,15</sup> as to whether oxalic acid is also one of the products. Loss of absorption at 268 nm after oxidation of viomycin with iodine in bicarbonate solution (reaction 3) showed that the chromophore was being oxidized.<sup>15</sup>

A model for the chromophore, a crystalline ureide (4) of dehydroserine,<sup>26</sup> has been synthesized by Johnson *et al.*<sup>27</sup> that supports the postulate that 1 is the chromophore. Data presented in Table I<sup>27</sup> compares the properties of 4 with those of viomycin.

Table I			
UV Spectra	Viomycin	<u>4</u>	
neutral/acid	267 nm ( $\epsilon$ 24,000)	266 nm ( $\epsilon$ 22,100)	
NaOH/H <sub>2</sub> O	290 nm ( $\epsilon$ 15,000)	308 nm ( $\epsilon$ 24,000)	



The nonexchangeable proton in the model appears at  $\delta$  7.8 ppm (CD<sub>3</sub>SOCD<sub>3</sub>/D<sub>2</sub>O) in its nmr, corresponding to viomycin's absorption at  $\delta$  8.1 ppm (D<sub>2</sub>O), and is assigned to the vinyl proton. The pK<sub>a</sub> value (12.6, in water) for 4 is identical with that of viomycin. Capreomycin IB<sup>24</sup> apparently also contains 1 as its chromophore.<sup>18,27</sup> Formation of the resonance-stabilized anions of the type 5 would account for the shift of the absorption maximum observed in the electronic spectrum upon addition of alkali to viomycin.<sup>10,27</sup> Reactions (1) and (2) of Fig. 2 were carried out on 4 and produced alanine and formylurea, respectively.

#### STRUCTURE OF VIOMYCINIDINE

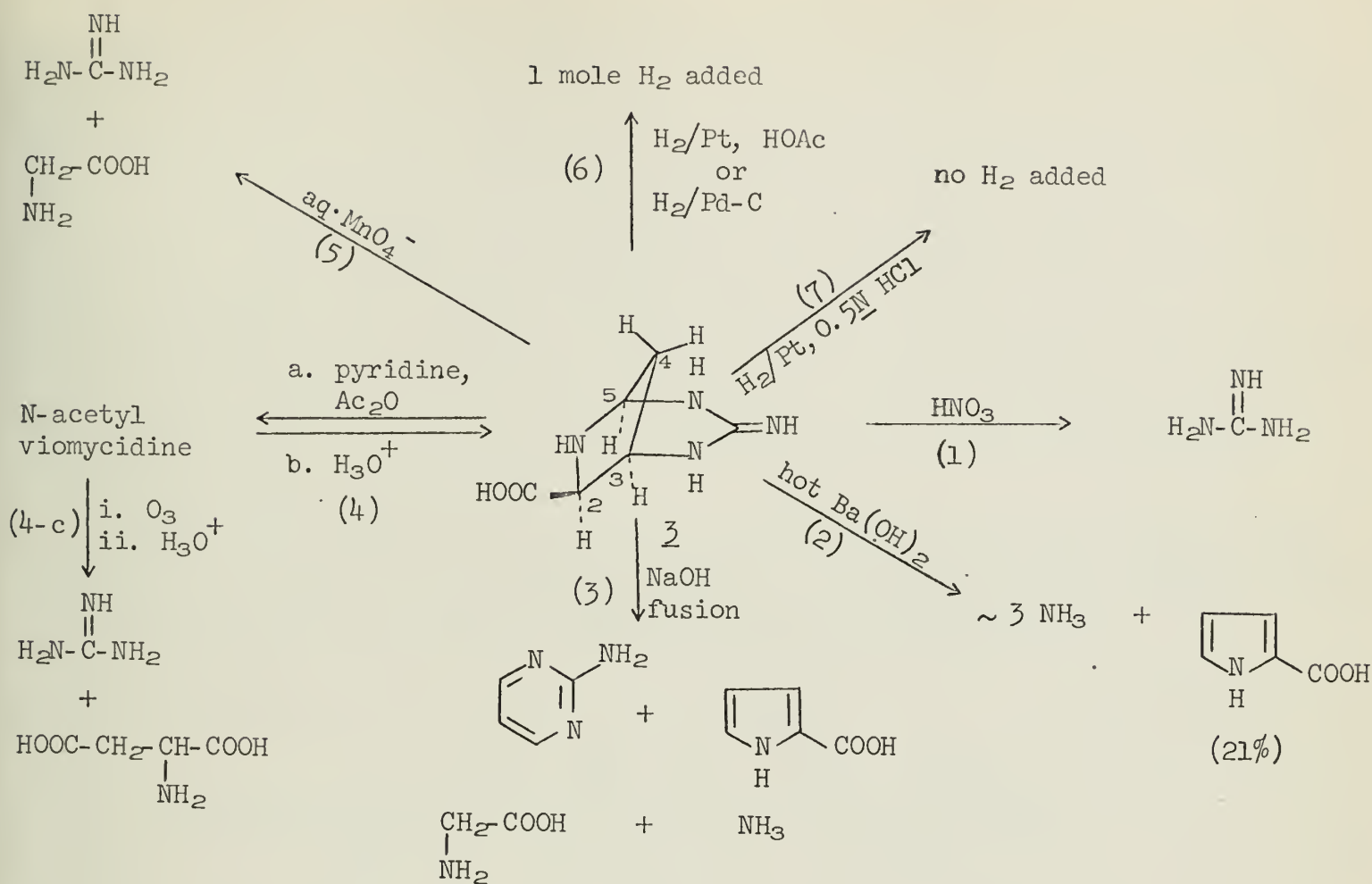
In 1966 Raleigh proposed 2,4,6-triaza-3-iminobicyclo[3.2.1]octane-7-carboxylic acid for the structure of viomycinidine, primarily on the basis of nmr data.<sup>28</sup> Numerous chemical data have supported Raleigh's structure<sup>12,29</sup> and X-ray crystallography<sup>21-23</sup> has confirmed it as structure 3 (see Fig. 3). Viomycinidine hydrochloride decomposes at 200-204° and has  $[\alpha]_{\text{D}}^{30}$  -78° ( $c$  1.78, in water). Potentiometric titration showed one carboxyl group, pK'<sub>D</sub> < 2.0; a secondary amine, 5.5, adjacent to the strongly basic guanidino group; and 12.6, a guanidino group.<sup>29,30</sup> The compound exhibited only end absorption in the uv.<sup>30</sup> The nmr showed five nonexchangeable protons in D<sub>2</sub>O at  $\delta$  5.63 ppm (1 H, C<sub>5</sub>, triplet, J = 2.4 cps), 4.62 (2 H, C<sub>2</sub> and C<sub>3</sub>, multiplet), and 2.52 (2 H, C<sub>4</sub>, triplet, J = 1.9 cps).<sup>30</sup> In trifluoroacetic acid the spectrum was reported as  $\delta$  5.93 ppm (1 H), 4.95 (2 H), 2.77 (2 H) and 8.5-7.0 (guanidinium absorptions).<sup>30</sup> Takita and Maeda also reported the nmr of the free base in D<sub>2</sub>O.<sup>29</sup>

Some of the reactions viomycinidine (3) undergoes are shown in Fig. 3.<sup>29-31</sup> Loss of

\*Products for reactions (2) and (4) of reference 12 appear to have been interchanged in the publication.



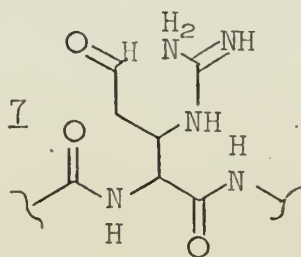
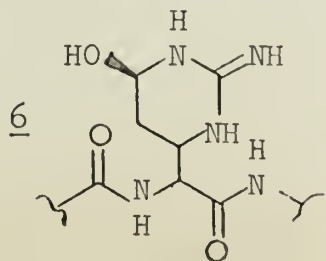
Fig. 3



guanidine (cf. reactions 1, 2, 3)<sup>30</sup> would form pyrrole-2-carboxylic acid. Guanidine could yield three moles of ammonia under the strenuous hydrolysis conditions of reaction (2). (Under similar conditions arginine yields two moles of ammonia.<sup>30</sup>) Similarly, pyrrole-2-carboxylic acid and ammonia could be produced by fusion of viomycin with sodium hydroxide.<sup>30</sup> Loss of glycine from viomycin and stabilization by aromatization would yield 2-aminopyrimidine. Structure **3**, however, does not explain the ozonolysis results of reaction (4).<sup>30</sup> Whether hydrogenation (reactions 6 and 7) of viomycin occurs is under dispute.<sup>29-31</sup>

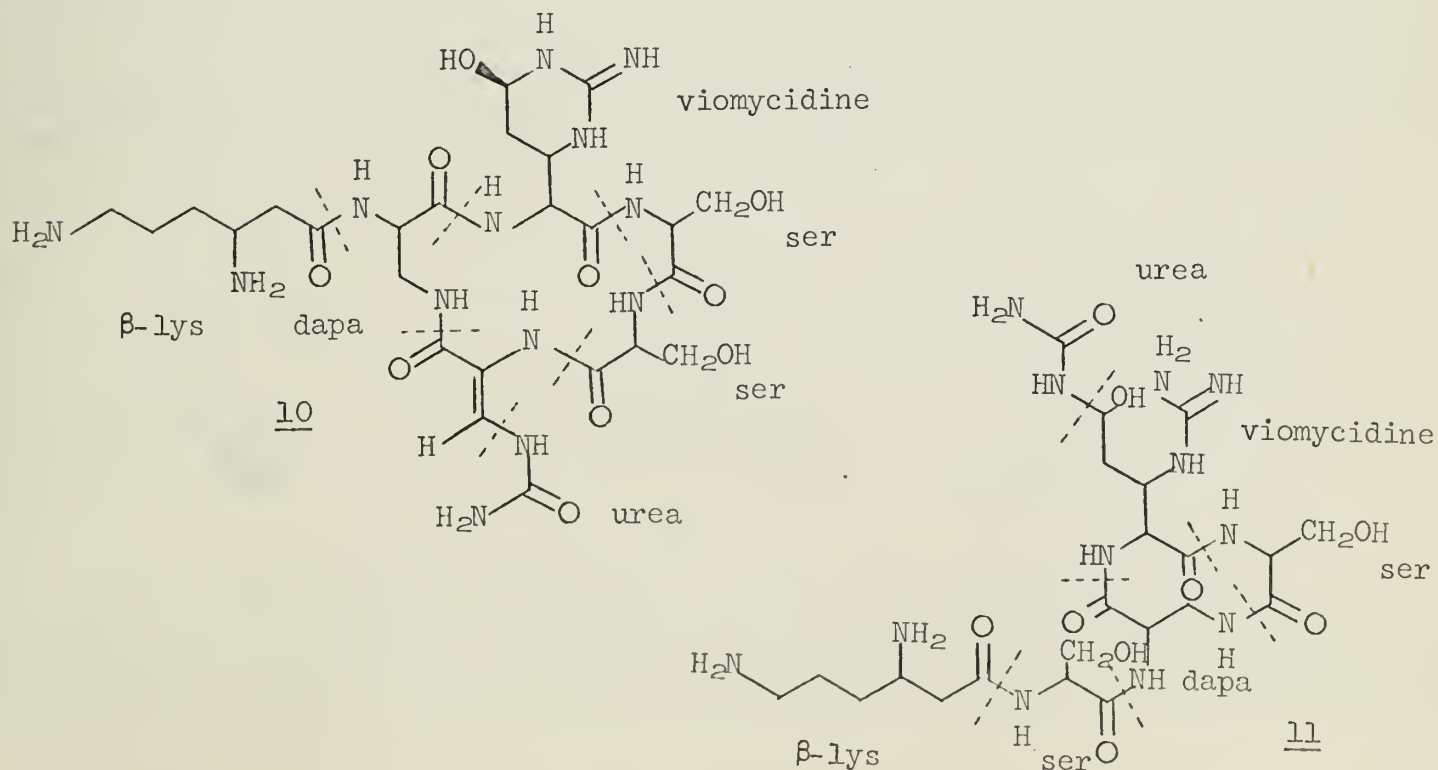
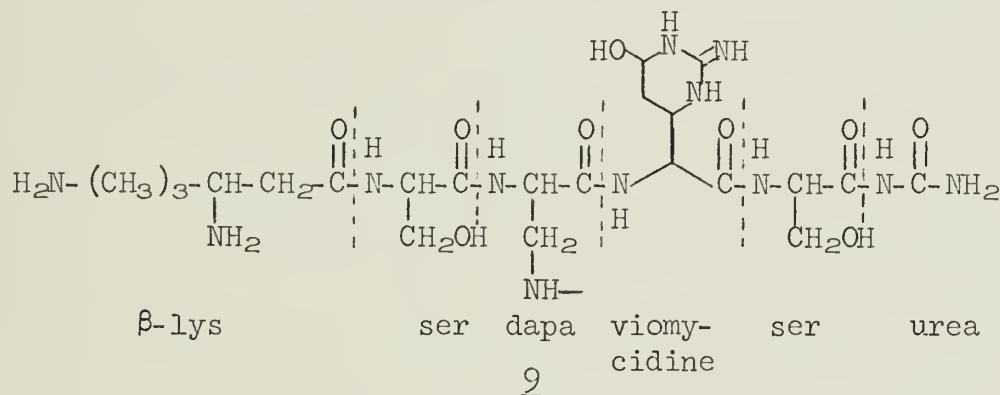
#### VIOMYCIN-PRODUCING MOIETY

Johnson and coworkers<sup>18, 20</sup> have suggested that **6** is the viomycin fragment that is acid hydrolyzed to give viomycin (**3**); and its equilibrium aldehyde form (**7**) yields the reduced product dihydroviomycin (**8**), (cf. reaction 4, Fig. 1). The equilibrium between **6** and **7** should allow the guanidine-carbinol center to adopt the most favorable configuration, *i.e.*, the hydroxyl group in a pseudo-equatorial position.<sup>20</sup> Lechowski<sup>32</sup> reported that transamidinase cleaved the amidine group of viomycin, suggesting a mono-substituted guanidino substituent in the molecule. An equilibrium between **6** and **7**, in which a free carbonyl group could condense with the primary amino group of the guanidine function or the amino group of the glycine moiety, would also help explain Mason's<sup>15</sup> obtaining three guanidino components from the acid hydrolysate and Kitagawa and coworkers'<sup>33</sup> finding three desureaviomycin fractions upon alkaline hydrolysis of viomycin. The fractions had the same amino acid sequence but showed different paper chromatographic and electrophoretic behavior and uv spectra.





Kitagawa and coworkers<sup>33</sup> were unable to duplicate the carboxypeptidase results. They proposed series 9 on the basis of standard end group analysis procedures. The position of urea was based upon desureaviomycin's possessing the free carboxyl group of a serine residue (determined by hydrazinolysis of desureaviomycin).





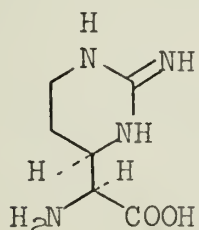
Johnson and coworkers<sup>12</sup> confirmed the structure of the fraction  $\alpha, \beta(-NH-)$ -diaminopropionyl·viomycidyl, and indicated that results as yet unpublished also supported serine's being attached to the viomycidine moiety. Controlled acid hydrolysis of desureaviomycin produced a peptide but no free amino acids, indicating only ring-opening of a cyclic structure. The peptide incorporated the free amino groups of  $\beta$ -lysine, the  $\beta$ -amino group of diaminopropionic acid, and the free carboxyl group of serine, indicating ring-opening resulting from hydrolysis of peptide bonds involving the  $\beta$ -amino group of diaminopropionic acid and the carboxyl group of serine. From these results it was concluded that the chromophore moiety was attached to the  $\beta$ -amino group of diaminopropionic acid. Including the seryl·seryl unit of Dyer *et al.*,<sup>10</sup> which had been substantiated by unpublished work, Johnson *et al.* proposed 10 as the structure of viomycin.

Based essentially upon the work of Dyer<sup>10</sup> and Kitagawa<sup>33</sup> and coworkers, Lechowski<sup>32</sup> proposed 11 as the amino acid sequence of viomycin. It differs from sequence 9 only in urea's not being attached to a serine moiety and both amino groups of  $\alpha, \beta$ -diaminopropionic acid being given attachment sites.

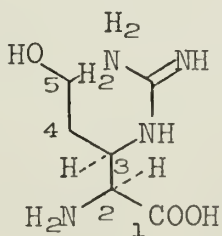
# STRUCTURE OF VIOMYCIN

Under varying conditions, viomycin gives several degradation and hydrogenation products, as shown in Fig. 1. For two of the products, 3 and 12, X-ray crystallographic analyses have confirmed their gross and stereochemical structures.

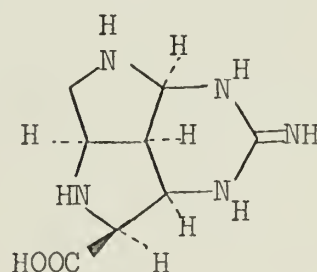
The products of reaction (1)<sup>15, 16, 30, 35, 36</sup> (6 *N* hydrochloric acid, reflux, 6 hr) resulted from hydrolysis of peptide bonds. Upon mild alkaline hydrolysis (0.1 *N* NaOH, 100°, 20 hr<sup>18</sup>) of viomycin (reaction 2), viomycidine (3) from the acid hydrolysate was replaced by 2-aminopyrimidine and glycine.<sup>12</sup> This result was corroborated by the formation of 2-aminopyrimidine, pyrrole-2-carboxylic acid, glycine, and ammonia upon sodium hydroxide fusion of viomycidine.<sup>30</sup> The products would be formed in essentially the same way as in the case of viomycidine by the formation of viomycidine or a viomycidine-like intermediate. Catalytic hydrogenation of viomycin (reaction 3)<sup>12, 18, 20</sup> gave urea and a perhydro derivative, which was hydrolyzed to L-serine, L- $\alpha, \beta$ -diaminopropionic acid, L- $\beta$ -lysine, capreomycidine (2), and alanine (product ratio, 2:1:1:1:1). Removal of the hydroxyl group of the viomycidine-producing moiety (6) by hydrogenolysis precludes cyclization between the amino group of the glycine moiety and the guanidino-carbinol system to form viomycidine. Thus, capreomycidine rather than viomycidine is formed. The capreomycidine product had ir, nmr, and ord spectra and tlc behavior<sup>20</sup> identical with an authentic sample isolated from the acid hydrolysate of capreomycin.<sup>24, 37, 38</sup> As would be expected, viomycidine itself has not been successfully converted into capreomycidine.<sup>18</sup>



2



8



12

Excess aqueous sodium borohydride (reaction 4)<sup>29</sup> converted viomycin to dihydroviomycin, which could not be differentiated from viomycin by comparing results from paper chromatography or electrophoresis or uv spectra. Dihydroviomycin's nmr differed from that of viomycin only by having two additional protons at  $\delta$  3.7 ppm (multiplet).



Dihydroviomycin (8), serine,  $\beta$ -lysine,  $\alpha, \beta$ -diaminopropionic acid, urea, carbon dioxide, and ammonia were liberated from dihydroviomycin upon total acid hydrolysis. Thus, sodium borohydride reduces the moiety in viomycin which produces viomycin upon acid hydrolysis. This fact, combined with the uv spectral identities for viomycin and dihydroviomycin, show that they have the same chromophore, which is not reduced by sodium borohydride and exists in the molecule independently from the viomycin-producing group. Potentiometric titration of dihydroviomycin ( $pK < 2.0, 7.4, > 12.0$ ) indicated one carboxyl group and two basic functions. One primary amino group was indicated by the Van Slyke method. Positive qualitative tests indicated primary amino and guanidino groups. The nmr assignments for 8 were  $\delta$  3.96 ppm (1 H, C<sub>2</sub>, doublet, J = 4 cps), 4.35 (1 H, C<sub>3</sub>, triple doublets, J = 4, 5, 9 cps), 1.92 (2 H, C<sub>4</sub>, multiplet), 3.76 (2 H, C<sub>5</sub>, multiplet) in D<sub>2</sub>O. The physical data for dihydroviomycin fits that expected for L-threo- $\beta$ -guanido- $\delta$ -hydroxy-n-valine (8).<sup>20, 21</sup> To substantiate 8 as the structure of dihydroviomycin, it was treated with acetyl chloride in 6 N hydrochloric acid and acetic acid (1:1 v/v)<sup>39</sup> to yield the O-acetyl derivative, confirmed by ir absorption at 1735 cm<sup>-1</sup> (KBr) for the monohydrochloride. The dihydrochloride's nmr spectrum indicated acetyl protons at  $\delta$  2.13 ppm (3 H, singlet) and acetoxymethylene protons at  $\delta$  4.12 - 4.0 ppm (2 H, multiplet) of the dihydrochloride, and that of  $\delta$  3.76 ppm (2 H, C<sub>5</sub>, multiplet) of the monohydrochloride of dihydroviomycin.

Two basic amino acids, viomycin (3) and viocidin acid (12) were isolated from the acid hydrolysate (reaction 5, 10 N hydrochloric acid, reflux, 24 hr).<sup>20</sup> The viocidin acid dihydrobromide was used in X-ray analysis to establish the complete structure and absolute stereochemistry as shown in 12.<sup>20</sup> Since the grouping  $\alpha, \beta$ -diaminopropionyl-viomycin has been well established, viocidin acid must be formed by condensation of the  $\alpha$ -amino group of diaminopropionic acid with the carbinol unit of 6 and the carbonyl group of the diaminopropionic acid residue with the carbon adjacent to the carbinol carbon. Apparently the  $\alpha, \beta$ -diamino grouping weakens the  $\alpha, \beta$  carbon-carbon bond sufficiently for it to be cleaved by strong acid.

Heating viomycin hydrochloride with methanol (reaction 6) produced the O-methyl derivative,<sup>40</sup> indicating that form 6 of viomycin is the more stable in hot alcoholic solution.

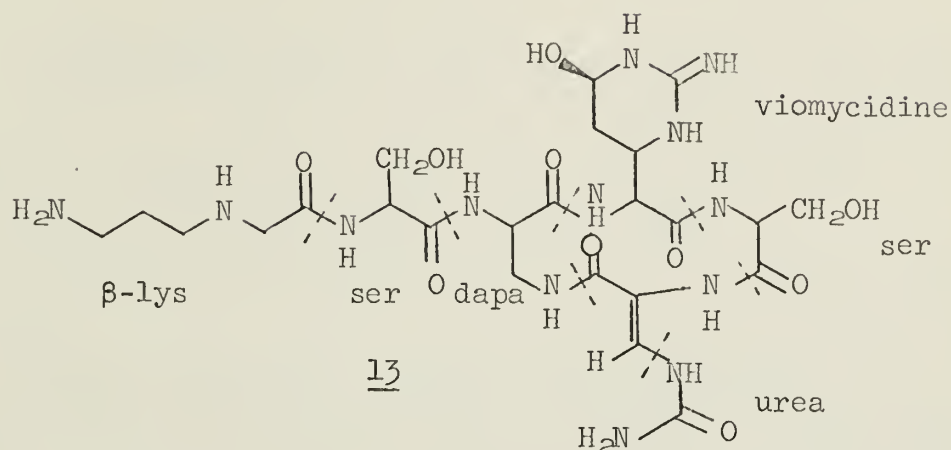
## SUMMARY

No completely satisfying structure of viomycin has been published. Structures 9, 10, and 11 satisfy the structural requirements for the reactions involving the viomycin-producing moiety, assuming the equilibrium between 6 and 7, since all three are essentially the same in that area of the molecule. In 11 the carbinol carbon must first be oxidized to a carbonyl group with the loss of urea to form 7. Neither 9 or 11 account for the uv spectra of viomycin. Urea itself does not absorb significantly at 268 nm,<sup>41</sup> thus it must be conjugated with some chromophoric group (cf. 5). Johnson et al. presented strong evidence for 1 as the chromophore and incorporated it into 10. But if 10 shows the antibiotic's structure in the vicinity of the chromophore, what happens to the remainder of the chromophore upon hydrolytic loss of urea? More specifically, what happens to the hydrolysis products of the unit that produces alanine upon hydrogenation and hydrolysis? Production of carbon dioxide, ammonia, and traces of glycine could not account for it. None of the structures account for the carbon dioxide and ammonia formed upon hydrolysis; however, ammonia may result from too vigorous hydrolytic conditions.

Based upon the painstaking and careful work presented by Kitagawa,<sup>33</sup> a more likely structure for viomycin might be 13. It differs from 10 only in the placement of a serine residue, thus its degradation products should be the same as those for 10 except for the amino acid sequence. Unfortunately this structure also suffers from an inability to explain the fate of the entire chromophore upon acid hydrolysis.



Unless these problems can be solved the complete structure of viomycin may have to await elucidation by synthesis or X-ray analysis.



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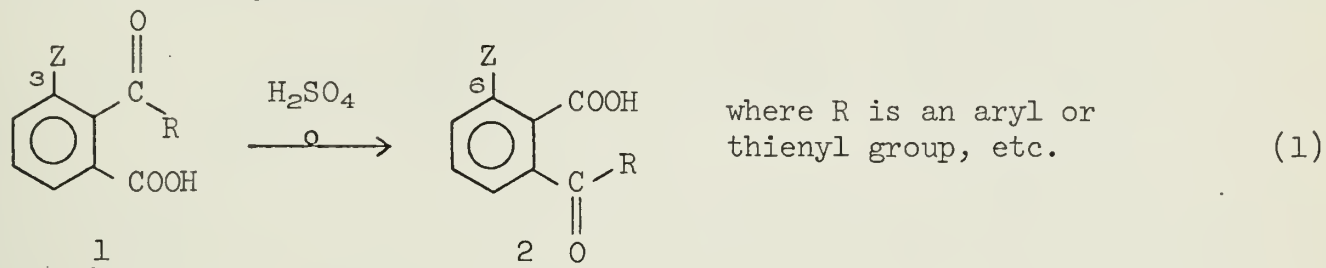
# THE HAYASHI REARRANGEMENT

Reported by Pak-Tong Leung

December 11, 1969

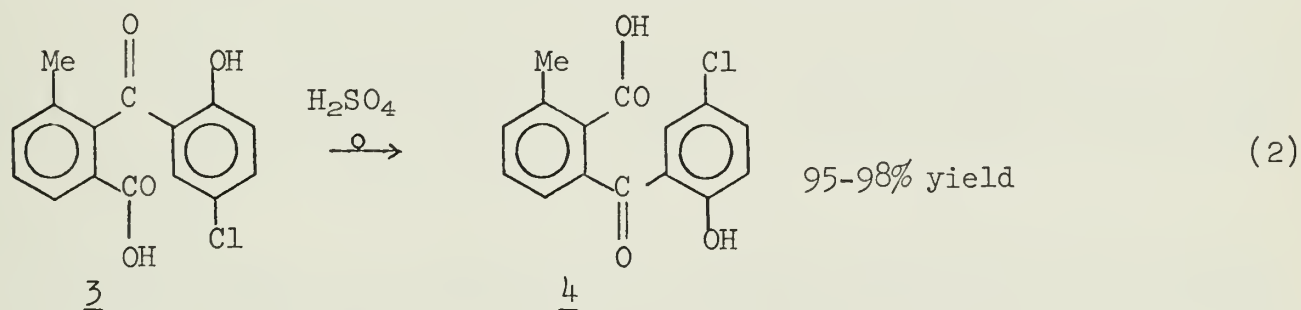
## INTRODUCTION

Normally 2-arylbobenzoic acids cyclize in sulfuric acid to give anthraquinones; however, in certain cases where the aryl group is activated or where there is a substituent in the 3-position of the benzoic acid ring, a 1,4 aryl migration takes place. This kind of intramolecular rearrangement, called Hayashi rearrangement, can be represented in a general equation as:



This seminar will follow the development of mechanistic investigations of the Hayashi rearrangement and cover some interesting chemistry of 2-arylbobenzoic acids related to this rearrangement.

The first case of this molecular rearrangement was reported in 1927 by Hayashi<sup>1</sup> in the course of the ring closure of certain substituted 2-benzoylbenzoic acids, e.g., chlorohydroxybenzoyltoluic acids. Instead of forming the ring closed product, he found that compound 3 rearranged to compound 4 on treatment with 98% sulfuric acid.

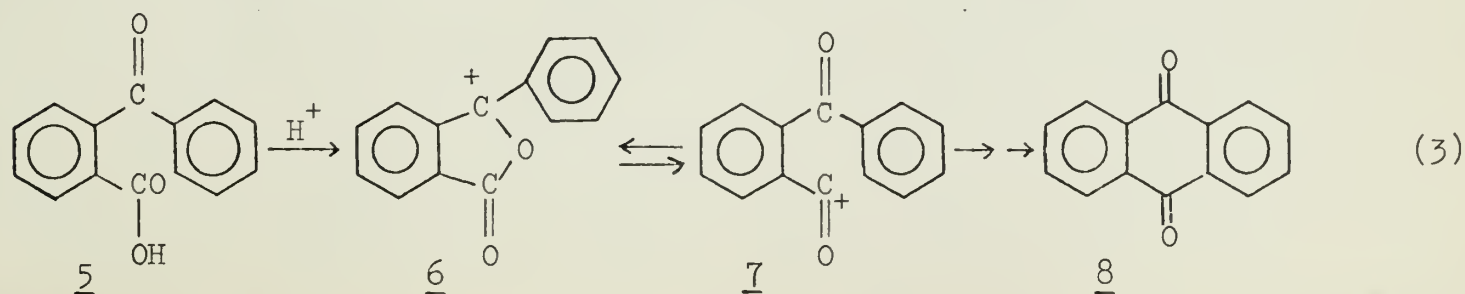


Since then, more instances of this type of intramolecular change have been found.<sup>2-7</sup> However, the nature of the mechanism of the rearrangement was not certain until 1956.<sup>1,2</sup>

## MECHANISTIC STUDIES

### I. Sandin's Scheme:

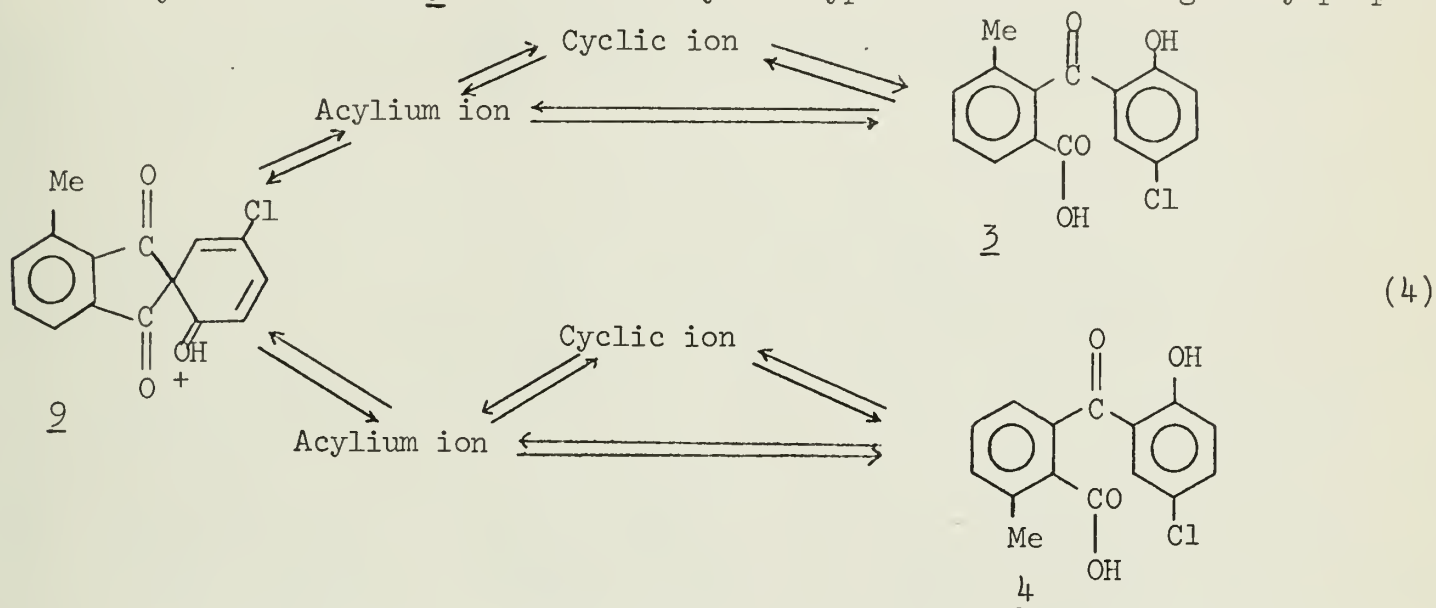
The interesting work of Newman,<sup>8</sup> on the intramolecular acylation of 2-benzoylbenzoic acid to anthraquinone in sulfuric acid, furnishes an important basis for understanding the Hayashi rearrangement. The cyclization is remarkable because it involves intramolecular acylation ortho to a ketonic function; ordinarily<sup>9</sup> ketones are not amenable to Friedel-Crafts acylation at any position. Newman<sup>8</sup> suggested that the reaction proceeds through the cyclic carbonium ion 6 and the acyl carbonium ion 7 which cyclizes to yield the anthraquinone 8. The presence of the lactyl cation





is supported by the fact<sup>10,11</sup> that when a cold solution of 2-benzoylbenzoic acid in 98% H<sub>2</sub>SO<sub>4</sub> is poured into methanol, the chief product is the pseudo ester 30. Isotope effect in the condensation of 2-benzoylbenzoic acid-9-C<sup>14</sup> in conc. H<sub>2</sub>SO<sub>4</sub> has been studied. Ropp<sup>15</sup> reported that k(12)/k(14) is 1.03 to 1.04.

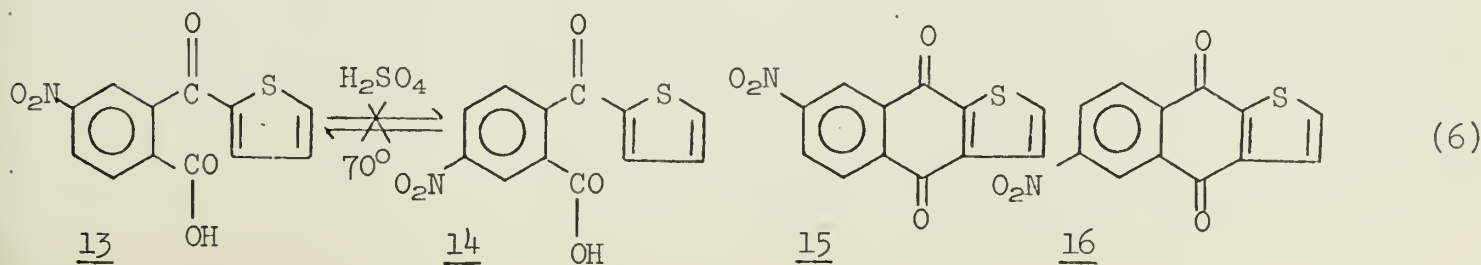
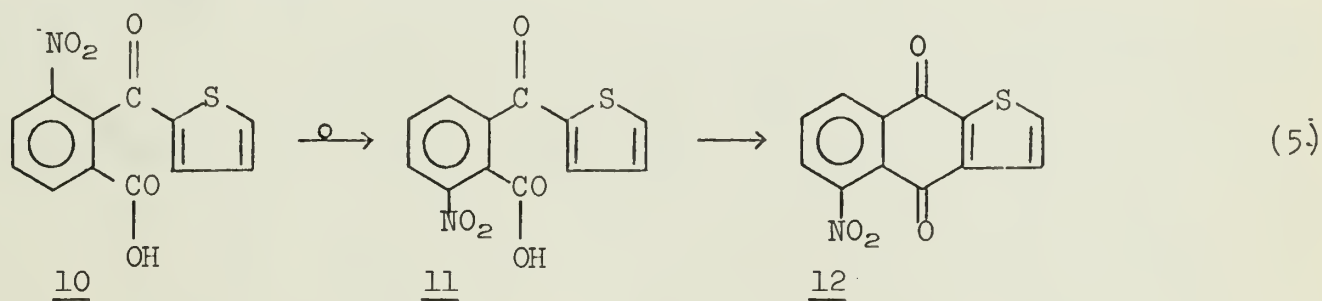
In view of Newman's evidence for acylium and cyclic ions, Sandin and co-workers<sup>12</sup> (1956) considered that the mechanism for the Hayashi rearrangement involves the interconversion of acylium ions through the bridged "phenonium" cation type structure 9. The key intermediate 9 is essentially the type of substance originally proposed



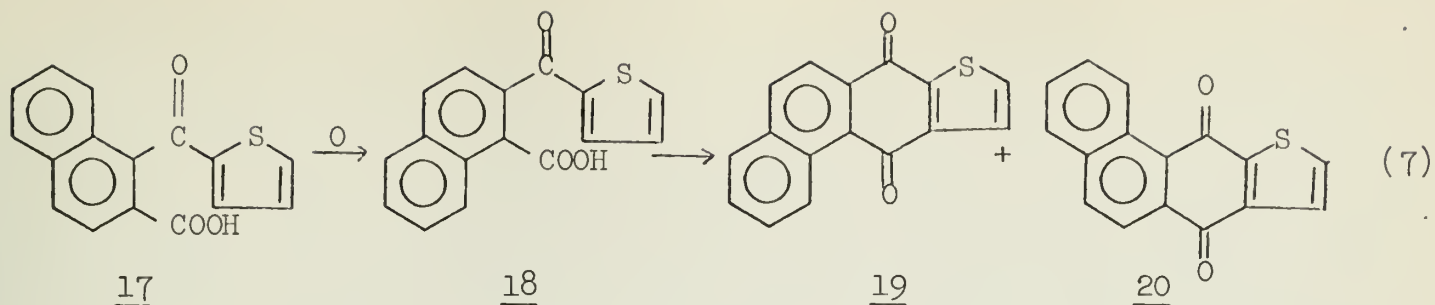
by Hayashi<sup>1</sup> to account for the rearrangement and is reaffirmed by Sandin.<sup>12</sup> However, in their study there is no experimental evidence to indicate the role of 9 in the rearrangement. It is possible that 9 is simply a transition state through which the acyl carbonium ions interconverted.

## II. Newman's Scheme:

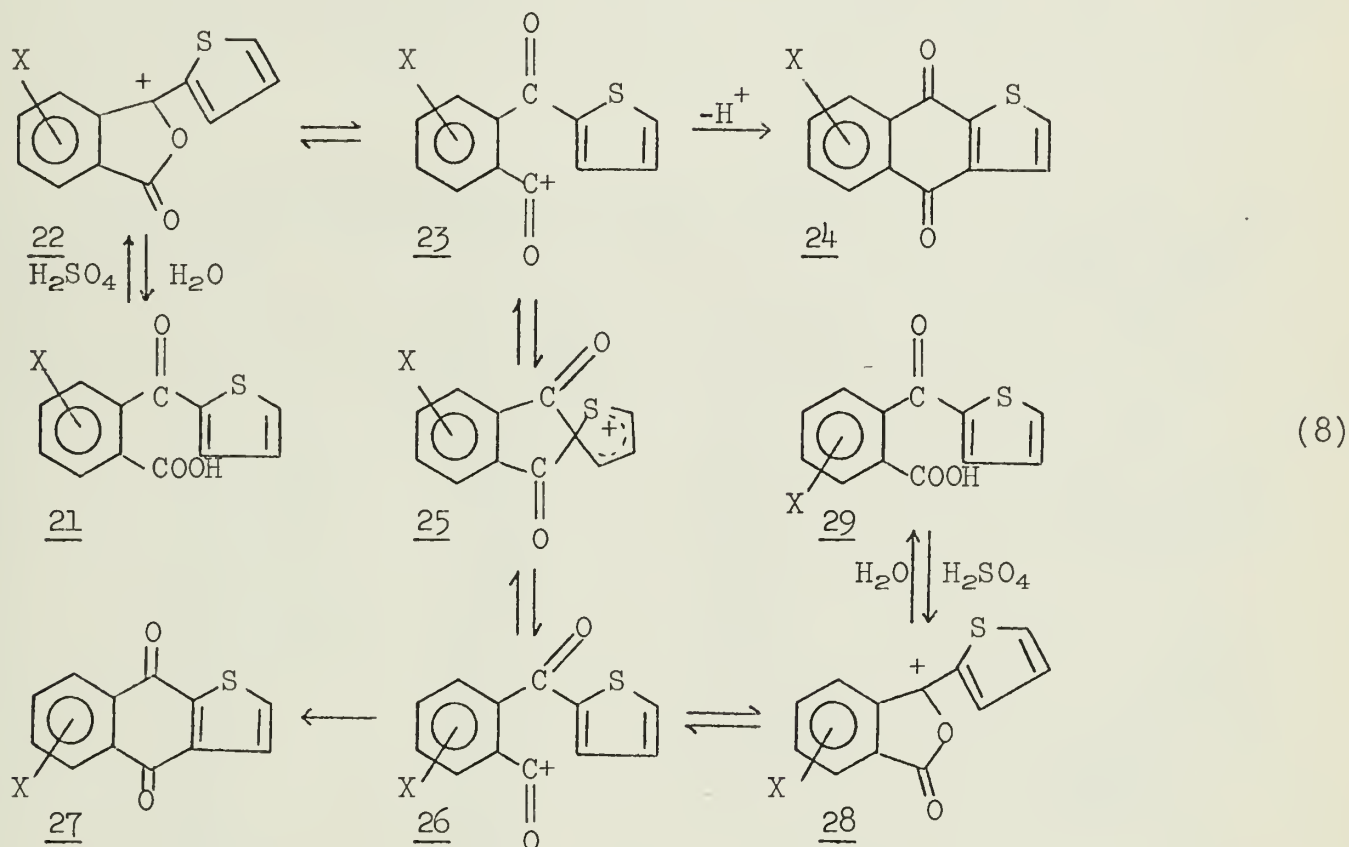
In the careful study on the behavior of 2-aryoylbenzoic acid in acidic media, Newman and Ihrman<sup>13</sup> have found that 10 rearranges to 11 (54% yield) in 100% H<sub>2</sub>SO<sub>4</sub> for 30 minutes at 70°, contrary to two previous reports<sup>6,7</sup> of other results. At a higher temperature (135°, 2 min) both 11 (34%) and 12 (27%) were obtained. Both 13 and 14 were recovered unchanged on treatment with 100% H<sub>2</sub>SO<sub>4</sub> at 70° whereas at a higher temperature (170°, 3 min) the same mixture of about equal amounts of 15 and 16 was formed from either 13 or 14. On heating 17 in 100% H<sub>2</sub>SO<sub>4</sub> at 60° for 1 hour, 18 was formed in 90% yield, whereas the rearrangement of 18 to 17 did not occur. At higher temperatures both 17 and 18 or a mixture of the two were converted to the same mixture of 19 and 20 (3:2).







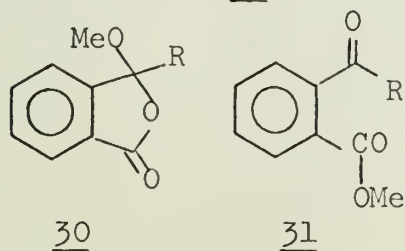
In order to clarify the behavior of the different keto acids and to aid predicting behavior of 2-arylbenzoic acids, Newman and Ihrman<sup>13</sup> elaborated Sandin's scheme<sup>5</sup> in more detail:



In the formulas above, X is any group ortho or meta (or both as in a ring fusion, e.g., naphthalene ring) to the nearer carbonyl group. Also instead of the thiophene ring, a substituted phenyl ring (or other unsymmetrical substituent) may be involved in the more general case.

### III. 2-Arylbenzoic Acids in Sulfuric Acid:

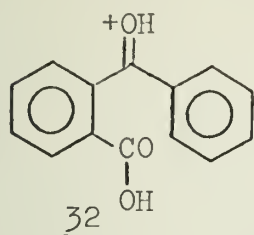
Newman, Kuivila and Garrett<sup>10</sup> studied the ionization of 2-benzoylbenzoic acid in 100% sulfuric acid in support of the earlier suggestion of Newman<sup>8,11</sup> that the dominant species in solutions is the cyclic ion. Newman and Ihrman<sup>13</sup> used the esterification of the keto acids and determined the amounts of the pseudo- 30 and normal esters 31 formed in order to estimate the amount of cyclic and acyl carbonium



ions present in the sulfuric acid solution. However, this method cannot be considered as accurate since Newman and Courduveliv<sup>16,17</sup> recently pointed out the fact that the composition of the ester formed under kinetic control is different from that formed under thermodynamic control in almost all cases. For the parent 2-benzoylbenzoic acid 5, the pseudo ester is formed more rapidly than the normal ester whereas the normal ester is formed exclusively under thermodynamic control (in methanolic hydrogen chloride solution).



Direct observation of the ionization of 2-benzoylbenzoic acid 5 in  $\text{H}_2\text{SO}_4$  solutions by spectroscopic methods has been carried out by Vinnik and co-workers.<sup>19</sup> They observed ionization to the extent of zero% in 85%  $\text{H}_2\text{SO}_4$ , 50% in 96%  $\text{H}_2\text{SO}_4$ , and 100% in 100% acid. The ionization of the keto acid results in the formation

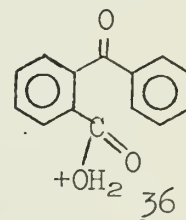
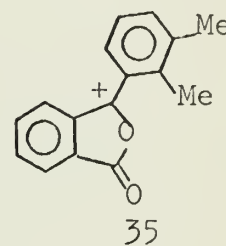
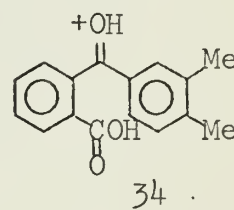
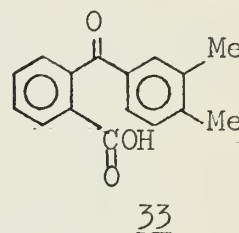


of three species at equilibrium: namely, the unionized keto acid BOH (5), the protonated form  $\text{BOH}_2^+$  (32), and the dehydrated form  $\text{B}^+$  (the lactyl ion 6). The reaction shows first-order kinetics. Since the reactive form  $\text{B}^+$  (6) of 2-benzoylbenzoic acid 5 has an absorption maximum at 410 m $\mu$ , its concentration can therefore be determined spectrophotometrically. Vinnik and co-workers<sup>19,20</sup> calculated the relative concentrations of the three forms of 2-benzoylbenzoic acid 5 and 2-(3',4'-dimethylbenzoyl)benzoic

acid 33 at various concentrations of  $\text{H}_2\text{SO}_4$  at 25° in terms of ionization constants,  $H_0$ ,  $J_0$ , and  $J_0^*$  (denoted by  $C_0$  by Deno, *et al.*<sup>14</sup>) functions, etc. Since assumptions have to be made during calculations, the values presented<sup>19,20</sup> may not be very accurate, but a trend of relative concentrations is clearly seen (see Table I).<sup>20</sup>

Table I. The Fractional Concentrations of Three Forms of 2-(3',4'-dimethylbenzoyl)benzoic Acid at Various Concentrations of  $\text{H}_2\text{SO}_4$  at 25°

$\text{H}_2\text{SO}_4$ , wt. %	$C_{\text{BOH}}$ ( <u>33</u> )	$C_{\text{BOH}_2^+}$ ( <u>34</u> )	$C_{\text{B}^+}$ ( <u>35</u> )
100			1.00
99	$1.2 \times 10^{-5}$	0.037	0.963
97	$1.7 \times 10^{-4}$	0.18	0.82
95	$6.8 \times 10^{-4}$	0.348	0.653
93	$2 \times 10^{-3}$	0.528	0.472
90	$7.4 \times 10^{-3}$	0.756	0.244
88	$1.6 \times 10^{-2}$	0.855	0.145
85	$4.4 \times 10^{-2}$	0.9	0.053
82	0.11	0.87	$1.9 \times 10^{-2}$
80	0.20	0.78	$1 \times 10^{-2}$
76	0.45	0.55	$2.7 \times 10^{-3}$
72	0.7	0.3	
70	0.82	0.18	
68	0.89	0.11	



Vinnik<sup>19</sup> recognized Newman's proposal<sup>8</sup> that acylium and lactyl ions exist in equilibrium and that the reactive form is acylium ion. Vinnik and co-workers,<sup>21</sup> therefore, assigned  $\text{B}^+$  as the acylium ion and  $\text{BOH}_2^+$  as the species protonated on the carboxylic group 36. These assignments have been shown<sup>23,24</sup> to be incorrect.

Noyce and Kittle<sup>23</sup> pointed out the fact that in about 80%  $\text{H}_2\text{SO}_4$  50% of the 2-benzoylbenzoic acid 5 is converted to the conjugated acid 32 with  $\lambda_{\text{max}}$  310 m $\mu$ . The nature of the spectral changes resulting on protonation and the sensitivity of the basicity to substitution both suggest that protonation occurs at the ketonic oxygen, but not the carboxylic oxygen, in accord with the fact that aromatic ketones are generally more basic than aromatic acids. Noyce and Kittle<sup>24</sup> further pointed out that the lactyl ion (with  $\lambda_{\text{max}}$  410 m $\mu$ ) is the best representation of 2-benzoylbenzoic acid in 100%  $\text{H}_2\text{SO}_4$ , but not the acylium ions as Vinnik mentioned.<sup>21</sup> The structure of lactyl ion is more in accord with the facts: A new absorption band at 410 m $\mu$  which appears in the solution of 2-benzoylbenzoic acid in  $\text{H}_2\text{SO}_4$  more concentrated than 90%, bears close resemblance to the visible band which characterizes the benzhydryl cation, formed when benzhydrol is dissolved in concentrated  $\text{H}_2\text{SO}_4$ .<sup>14,25</sup> Furthermore, the introduction<sup>24</sup> of electron-donating substituents *para* to the cation

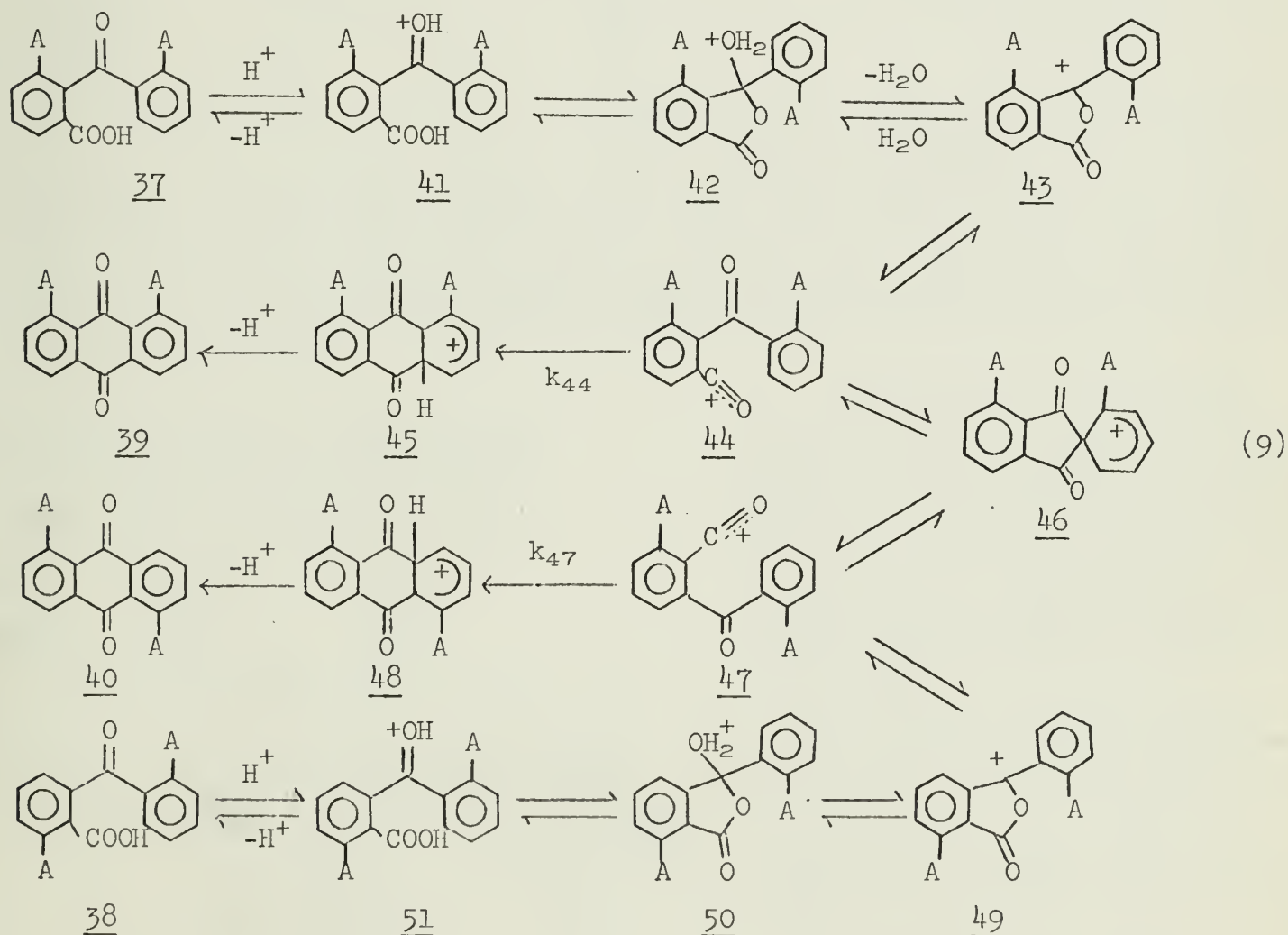


center results in a substantial bathochromic shift. This pattern of spectral changes is inconsistent with the acylium ion structure. The introduction of electron-donating substituents into the 4'-position or the 5-position results in analogous lactyl carbonium ions being formed at substantially lower  $\text{H}_2\text{SO}_4$  concentrations. Correlations of the effect of the structure on the ease of formation of the lactyl ion are best with  $\sigma^+$  values,  $\rho$  being 1.83. Such a result is inconsistent with a structure like the acylium ion and therefore supports the postulate that the lactyl carbonium ion is the dominant structure.

One therefore concludes that at high acid strength (e.g., 96-100%  $\text{H}_2\text{SO}_4$ ) the benzoylbenzoic acids exist in large part (or entirely) as the corresponding lactyl cation. On the other hand, in dilute acid solution, the acids exist as protonated species or as the free acids (See Table I). In other words, the ionization of 2-benzoylbenzoic acid in concentrated  $\text{H}_2\text{SO}_4$  involves protonation on the ketone (in about 80%  $\text{H}_2\text{SO}_4$ ) followed by a second stage involving loss of water (occurring in more concentrated  $\text{H}_2\text{SO}_4$ ) to give the lactyl carbonium ion.<sup>26</sup>

#### IV. Cristol's Scheme:

With the additional information about the ionization in 2-benzoylbenzoic acids,<sup>23,24</sup> Cristol and Caspar<sup>27</sup> extended the Sandin-Newman mechanism for the Hayashi rearrangement and Newman's mechanism<sup>8,29</sup> for anthraquinone formation in more detail during their study of the preparation of 39 and 40 via sulfuric acid catalyzed ring closures of 37 and 38. They also observed that the Hayashi interconversion of acids



A = Methyl

39:40 = 1:4

37 and 38 occurs more rapidly in the strong acid medium than does anthraquinone formation. The ratio of quinones 39 to 40 formed (1:4) was substantially invariant over the range 70 to 96% sulfuric acid, even though the temperature of the anthraquinone formation reaction was varied from 100 to 30°. But the composition of the



apparent equilibrium mixture of 37 and 38 (as evidenced from the composition of the acid mixture obtained after work up) is very sensitive to the acid strength. To account for these results, they assumed that the formation of intermediate 46, the "phenonium ion," is the slow step in the Hayashi rearrangement, and the reaction forming intermediates 45 and 48 are product determining in the formation of 39 and 40, respectively, with all other steps being relatively fast ones. They further argued that although the concentrations of 44 and 47 are markedly dependent upon acidity, the ratio of  $[44]/[47]$  is independent of acidity. Thus, if  $k_{44}/k_{47}$  is relatively insensitive to medium effect and to the temperature, the ratio of anthraquinone products will be invariant. In low acid region, the free acids 37 and 38 (or their protonated forms 41 and 51) are at equilibrium.

#### THE EFFECT OF SUBSTITUENTS

The effect of both electron-withdrawing and electron-donating substituents at various positions in 2-benzoylbenzoic acid on the rate of formation of substituted anthraquinones has been studied by Noyce and Kittle.<sup>26</sup> The effects of substituents in the benzoyl ring show strong dependence upon the electron-donating ability of substituents in the 3'-position (using  $\sigma^+$ ,  $\rho = -5$ ). More striking is the observation that introduction of a 4'-methyl or a 4'-methoxy group causes a decrease in the observed rate of anthraquinone formation (See Table II<sup>26</sup>). This is attributed to the fact that the carbonium ion stabilizing the lactyl carbonium ion vis-a-vis the open-chain acylium ion.

Table II. Rate of Cyclization of 2-(X-Benzoyl)benzoic Acids at 25° in H<sub>2</sub>SO<sub>4</sub>

X	Relative Rate
H	1.00
3'-Methoxy	10,800
4'-Methoxy	0.0016
3'-Methyl	164
4'-Methyl	0.25
3',4'-Dimethyl	22

On the other hand, the influence of substituents in the phthaloyl ring is much more modest. 2-Benzoyl-5-methoxybenzoic acid reacts more slowly than the parent compound, while 2-benzoyl-5-nitrobenzoic acid reacts more rapidly. Again these data (see Table III<sup>26</sup>) show that the substituent makes the lactyl carbonium ion formed from 2-benzoyl-5-nitrobenzoic acid less stable relative to the transition state for anthraquinone formations than that formed from 2-benzoylbenzoic acid; it requires substantially higher concentrations of H<sub>2</sub>SO<sub>4</sub> to cause its formation. Once formed it is more reactive; hence the rate for 2-benzoyl-5-nitrobenzoic acid is larger.

Table III. Rates of Cyclization of 2-Benzoyl-X-benzoic Acid at 60°

X	H <sub>2</sub> SO <sub>4</sub> , %	Relative Rates
H	99.10	1.00
5-OCH <sub>3</sub>	96.19	0.089
5-NO <sub>2</sub>	95.48	0.19
	100.1	4.0

Table IV. Rates of Hayashi Rearrangement ( $k_R$ ) and Anthraquinone Formation ( $k_F$ ) in 2-Benzoyl-X-benzoic Acids at 72°, 10% Oleum

X	$10^4 k_R(\text{min}^{-1})$	$10^4 k_F(\text{min}^{-1})$
H	Not observable	100
4- or 5-CH <sub>3</sub>	Not observable	250
3-Cl	8,000	8.0
3-CH <sub>3</sub>	12,000	2.5
3,4-Benzo	22,000	4

It appears that the Hayashi rearrangement is largely restricted to 3- or 6-substituted 2-benzoylbenzoic acids or to situations in which the point of attachment of the phthaloyl moiety to the other aromatic system is a strongly activated aromatic site.<sup>26</sup>

#### HAYASHI REARRANGEMENT vs. ANTHRAQUINONE FORMATION

In order to understand the factors influencing the relative importance of the Hayashi rearrangement and anthraquinone formation in substituted benzoylbenzoic acids, Cristol and co-workers<sup>28,30</sup> carried out a comparison study. Their results are tabulated in Table IV.

From the above data,<sup>30</sup> it is obvious<sup>28</sup> that the 3-substituted species undergo Hayashi rearrangement about  $10^3$  times faster than their equilibrium mixtures undergo



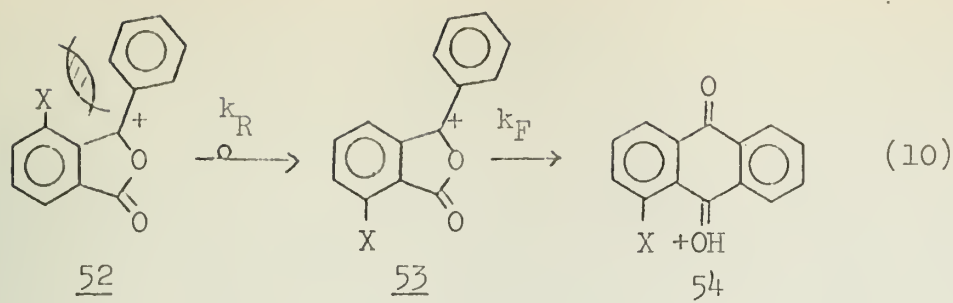
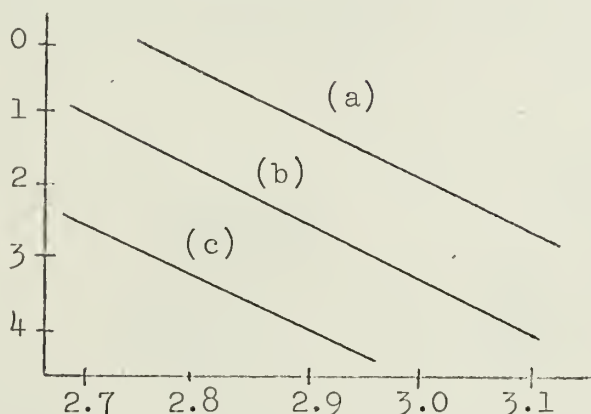


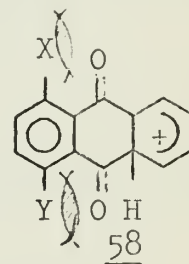
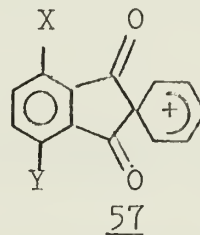
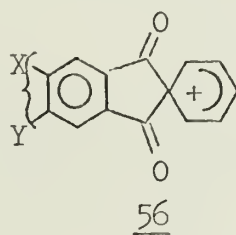
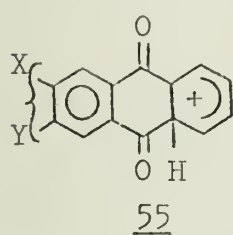
Figure I. Summary of Rate Data for Methyl Derivations of 2-Benzoylbenzoic Acid



(a) Hayashi rearrangement 3→6-CH<sub>3</sub>; (b) Anthraquinone formation 4- and 5-CH<sub>3</sub>; (c) Anthraquinone formation 6-CH<sub>3</sub>

anthraquinone formation, while the unsubstituted (or the 4- or 5-substituted) acids give faster rates of anthraquinone formation but do not undergo observable Hayashi rearrangements, even though their rates of anthraquinone formation are about 200 times slower than the rates of rearrangement for the 3-isomers. The data were rationalized<sup>28,30</sup> by considering steric strain. The 3-substituted lactyl carbonium ions 52 release the steric strain between the 3-substituted group and the ortho-group of the phenyl ring by going to a sterically more stable lactyl carbonium ion 53. However, this is not the case in the 4- and 5-substituted lactyl carbonium ions. Thus the Hayashi rearrangement involves transformations that depend upon the relative stabilities of lactyl carbonium ions. As for the anthraquinone formation vs. Hayashi rearrange-

ment, it will depend upon the stability of the transition state (resembling phenonium ions) during the course of the reaction. In other words, since intermediate 54 is of lower energy than 55, the reaction proceeds to anthraquinone formation; and since intermediate 56 is of lower energy than 57, Hayashi rearrangement occurs.



#### REVERSE HAYASHI REARRANGEMENT

Reverse Hayashi rearrangements (6-substituted to 3-substituted isomers) in relatively dilute H<sub>2</sub>SO<sub>4</sub> have been observed by Cristol and co-workers<sup>27,28,30</sup> when they examined the effect of H<sub>2</sub>SO<sub>4</sub> concentration on Hayashi rearrangements. They showed that the apparent composition of the equilibrium mixture of 38 and 37 is

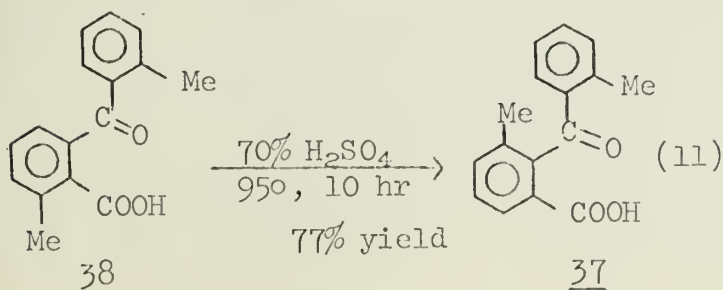
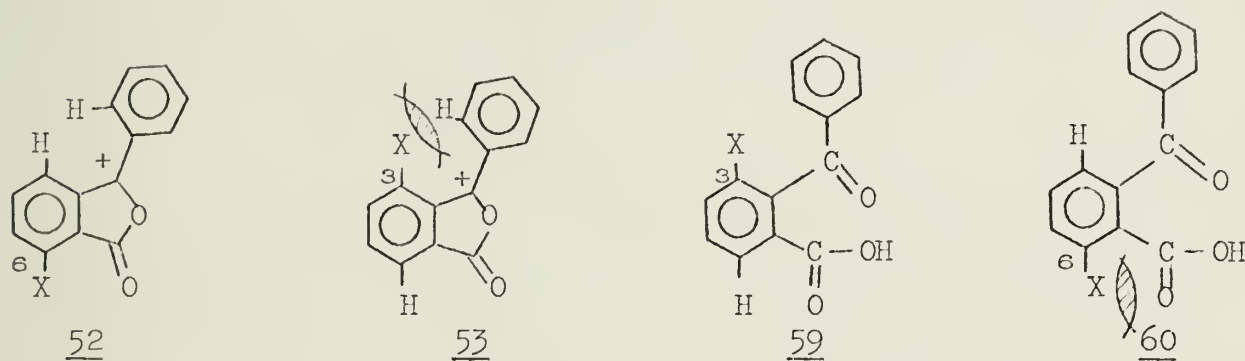


Table V. Effect of H<sub>2</sub>SO<sub>4</sub> Concentration upon Composition of Mixtures of 37 and 38

Starting Acid	% [H <sub>2</sub> SO <sub>4</sub> ]	Product
<u>37</u>	96	All <u>38</u>
<u>38</u>	96	All <u>38</u>
<u>38</u>	90	<u>38</u> and <u>37</u>
<u>38</u>	80	Largely <u>37</u>
<u>38</u>	70	All <u>37</u>



very sensitive to the acid strength (see Table V<sup>27</sup>). The products were identified by mixture mp and infrared spectroscopy. The results suggest<sup>27,28,30</sup> that the "normal" Hayashi rearrangement (3-substituted to 6-substituted keto acids) is observed in 96% H<sub>2</sub>SO<sub>4</sub>, while a "reverse" rearrangement (6-substituted to 3-substituted keto acids) is observed in the 70% H<sub>2</sub>SO<sub>4</sub>. A reasonable explanation<sup>27,30</sup> given by Cristol is based on the suggestion that the 2-benzoylbenzoic acids or their protonated forms have an order of stabilities opposite to those of the lactyl cations formed in more acidic medium. This is also a case where the ortho steric strain is important. In the lactyl carbonium ion, a 6-substituent (52) is more stable than the 3-substituent (53). Therefore, rearrangement occurs to obtain the more stable 6-substituted carbonium, namely, the "normal" Hayashi rearrangement. However, in the free acid a 3-substituent (59) is more stable than a 6-substituent (60). Therefore, rearrangement proceeds to give the more stable 3-substituted carbonium ion, namely, the "reverse" Hayashi rearrangement.



## CONCLUSION

A detailed mechanism for the Hayashi rearrangement has been worked out to account for the experimental facts and the basic nature of the intermediates has been investigated. The relative driving forces for the rearrangement and for anthraquinone formation are now understood. The fact that the Hayashi rearrangement is amenable to being driven in either direction may provide a useful synthetic device.

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# RING CONTRACTION OF CYCLIC SULFONES

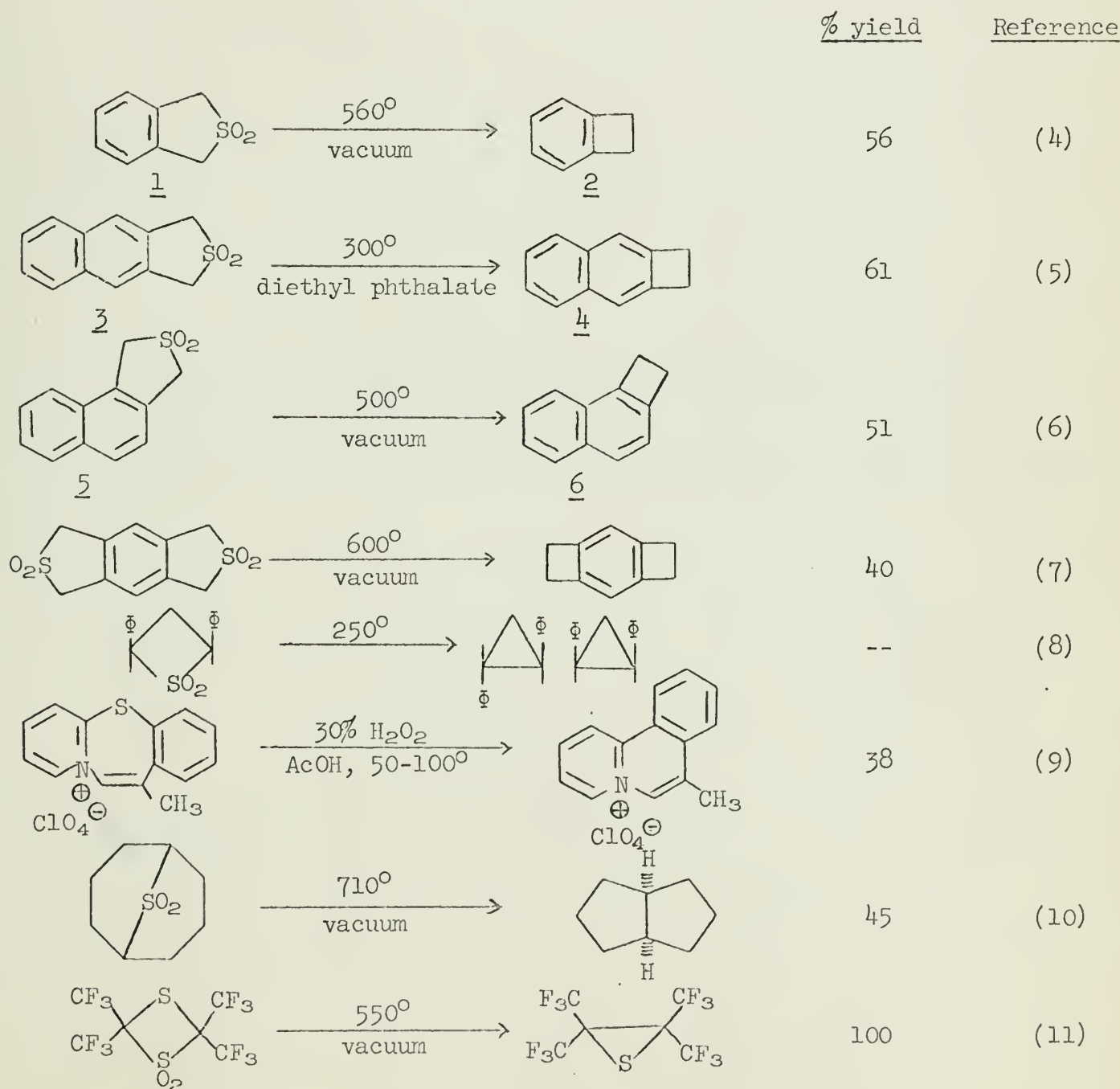
Reported by Marvin Raba

December 18, 1969

The synthesis of ring contracted compounds from cyclic sulfones has not found success in the hands of many. Three methods have been used to effect formation of a carbon-carbon bond between the  $\alpha$  and  $\alpha'$  carbons: pyrolysis, photolysis, and chemical reaction with Grignard reagents. A complete list of the synthetic achievements obtained through pyrolysis and photolysis has been compiled up to 1966.<sup>1</sup> The formation of alkenes from episulfones<sup>2</sup> and  $\alpha$ -halo sulfones<sup>3</sup> will not be discussed here.

## PYROLYSIS

The following ring contractions have been brought about with extrusion of sulfur dioxide by pyrolysis either in the gas phase or during distillation from solution. Reaction (9) occurs under conditions sufficient for oxidizing the sulfide to the sulfone.





Pyrolytic loss of sulfur dioxide from cyclic sulfones gives rises of the stereochemistry can be produced by the nature of opening predicted by the Woodward-Hoffmann rules for electrocyclic isomerization. Cis- and trans-2,5-dimethyl-1,2,5-dihydrothiophene-1,1-dioxane, 7 and 8, were prepared by reaction of sulfur dioxide with 2,4-hexadiene in ether. After separation on alumina, the stereochemistry of 7 was proven by the addition of bromine to give only one dibromide, which showed non-equivalent methyls in the nmr ( $\delta$  1.53 and 1.19), while 8 produced two isomeric dibromides with equivalent methyls ( $\delta$  1.53 and 1.51). Upon gas phase pyrolysis, 7 yielded trans, trans-2,4-hexadiene and 8 gave trans, cis-2,4-hexadiene.<sup>12,13</sup> This stereospecificity is consistent with a disrotatory opening process predicted for a system with  $4n + 2$   $\pi$ -electrons. A conrotatory opening is predicted for the  $4n$   $\pi$ -electrons involved during the pyrolytic opening of 9 and 10. Pyrolyzed in the



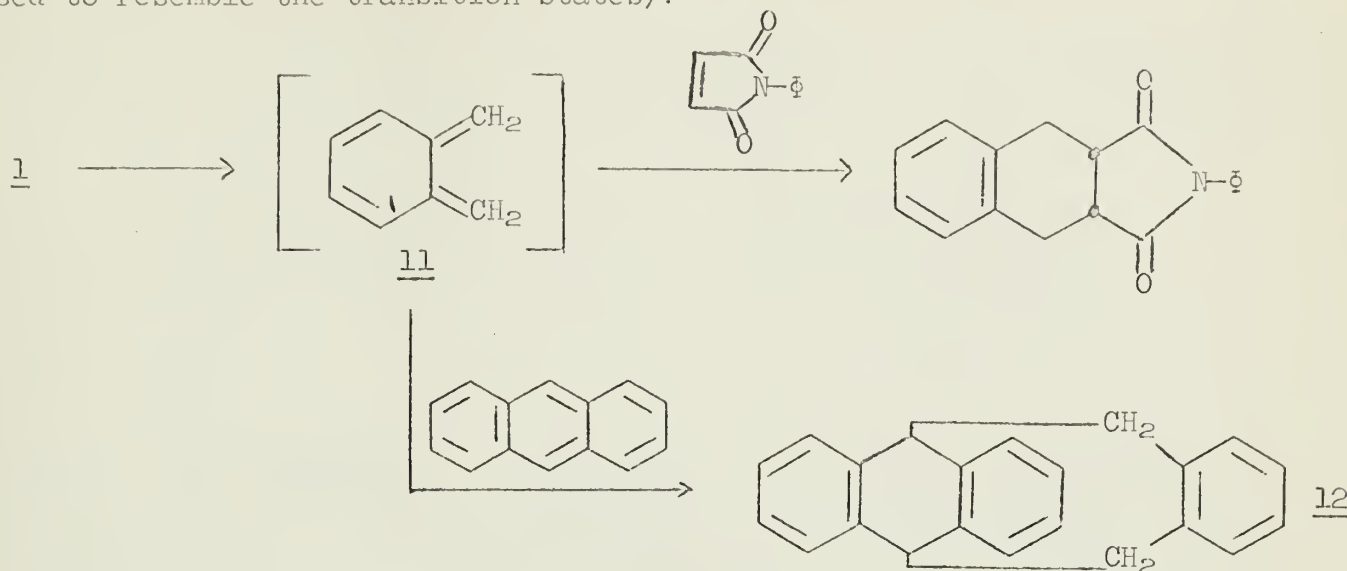
injection port of a gas chromatograph, 9 and 10 produce trans, cis, cis-2,4,6-octatriene and trans, cis, trans-2,4,6-octatriene respectively.<sup>14</sup> The stereospecificity of these openings rules out these pyrolyses proceeding through a triplet intermediate if one assumes that rotation about carbon-carbon bonds to produce a mixture of stereoisomers would proceed faster than electron pairing in a triplet.



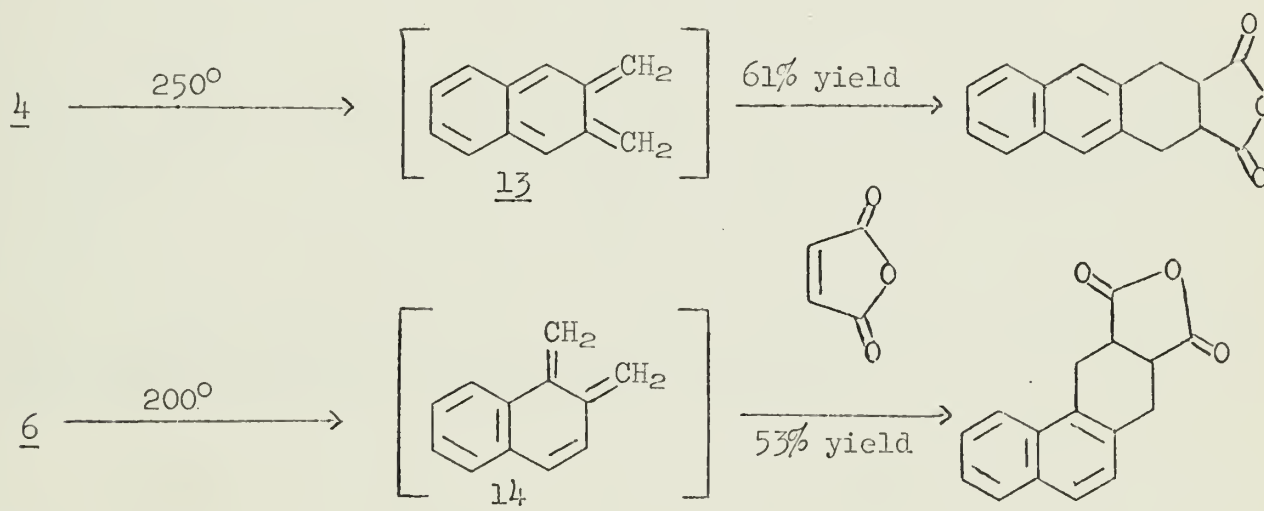
Gas phase pyrolysis of 1, 3, and 5 in the presence of 4-phenyl-1 radical affords Diels-Alder adducts to the exclusion of normal products and it was suggested that o-quinodimethanes were intermediates in the reaction. These o-quinodimethanes are highly reactive and a high degree of free radical character has been calculated<sup>15</sup> for the methylene groups of 11. When 1 is pyrolyzed with anthracene, which is



assumed to be a good trapper of benzyl free radicals, adduct 12 is formed.<sup>16</sup> The relative reactivities of the sulfones and ring contracted compounds are often explained by the stabilities of the corresponding ortho-quinodimethanes (which are supposed to resemble the transition states).



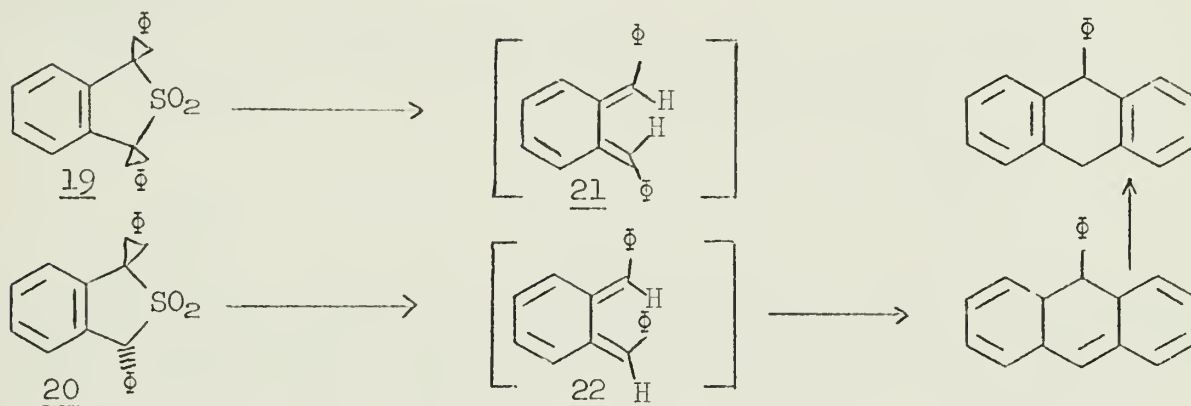
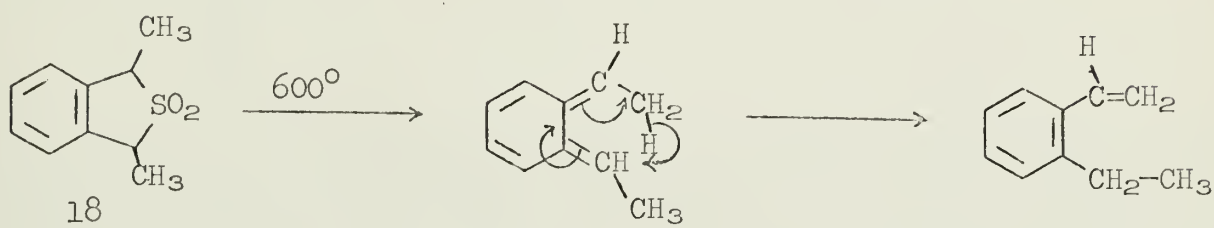
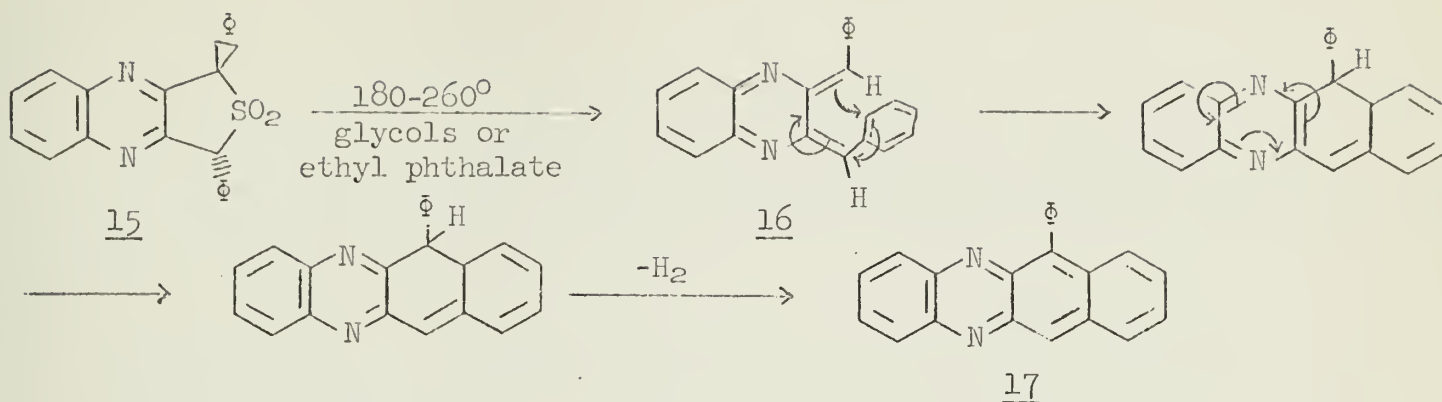
The sulfur dioxide extrusion reaction is reversible: 1 being reformed from benzocyclobutene and sulfur dioxide at 200 degrees.<sup>17</sup> Maleic anhydride trapping of the o-quinodimethane from the naphtho [b]cyclobutene, 4, requires a higher reaction temperature than the same reaction with naphtho[a]cyclobutene, 6.<sup>8</sup> This is explained if 13 and the more stable, partially benzenoid quinodimethane 14 approximate the rate-limiting transition states.



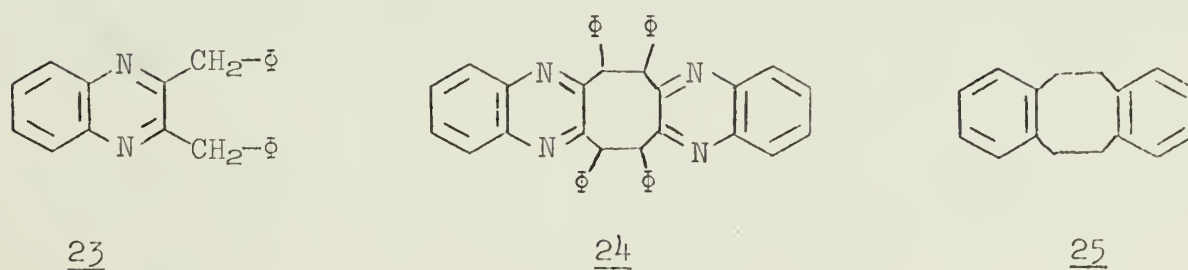
Three reactions compete with ring contraction: 1) intramolecular cyclization, 2) reduction, and 3) dimerization; and all can be explained by postulating an o-quinodimethane intermediate.

Intramolecular cyclization occurs with  $\alpha$ -substituted sulfones and is shown here for 15,<sup>18</sup> which consistently gives 17, 6-phenylbenzo[b]phenazine, in high boiling solvents and for 18,<sup>19</sup> which only yields o-ethyl styrene upon vacuum pyrolysis. Because both cis-20 and trans-21 19 and 20 give the same intramolecular cyclization product, the two stereoisomeric o-quinodimethane intermediates, 21 and 22, formed by disrotatory opening must be interconvertable. This interconvertability would be easily achieved under the energetic conditions of pyrolysis because of the low bond order in the exocyclic double bonds.



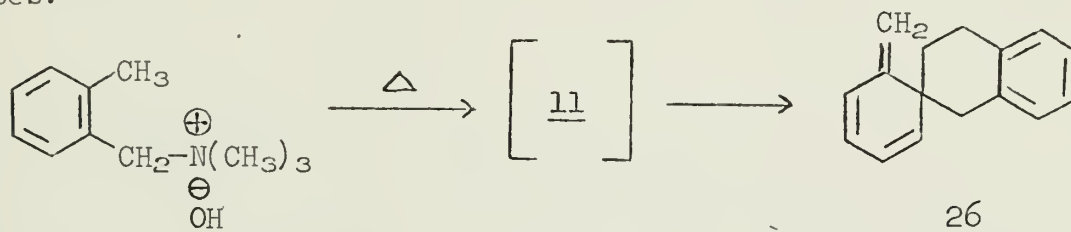


Only in protic solvents, such as the glycols, does reduction of 16 occur to give among the products 23, 2,3-dibenzylquinoxaline.<sup>18</sup>





Dimerization occurs at high temperatures in non-protic solvents. For example, 24 was formed from 15 in 27% yield at 550 degrees in solid sodium bicarbonate.<sup>18</sup> The nmr of 24 showing a singlet at  $\delta$  5.57 for four benzylic protons, and a bathochromic shift of 50 nm compared to the monomer in the uv suggest a tub form. In boiling ethyl phthalate, 1 yields only dimer 25, while 3 gives the ring contracted 4. This is consistent with the lower radical character of the benzoquinoid 11 relative to that of the naphthoquinoid 13 so that 11 is sufficiently unreactive to wait around for dimerization.<sup>5</sup> None of the possible spiro dimers, such as 26 which is formed when 11 is produced by other means,<sup>22</sup> have ever been isolated from sulfone pyrolyses.

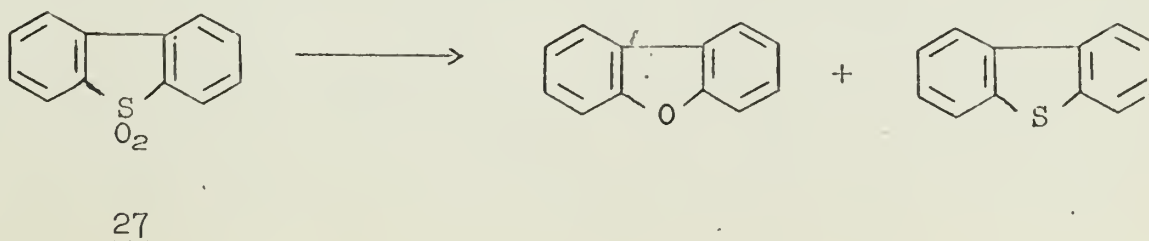


The rate of desulfonylation of 1 in the gas phase is independent of the reaction pressure; but the reaction pressure plays an important role in determining the fate of the ortho-quinodimethane intermediate.<sup>23</sup> As seen in Table 1, the same total product yield (ring contracted 2 plus dimer 25 plus o-xylene) is found at atmospheric pressure and 15 mm of Hg; but the fraction of dimer increases at the higher pressure.

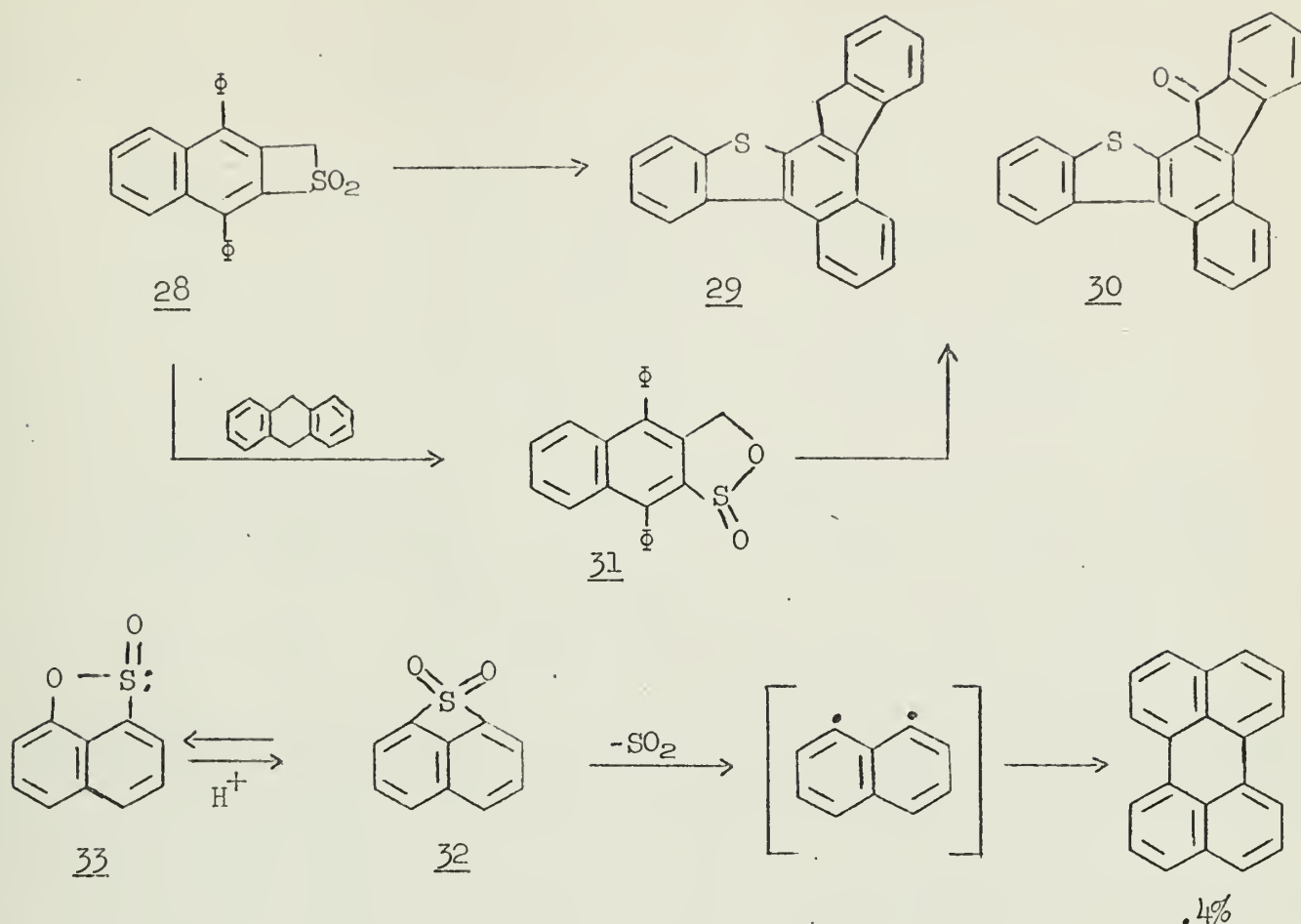
Table 1. Pyrolysis of 1 in the gas phase at 300 degrees.

Pressure	Percentage Yield		
	<u>2</u>	<u>25</u>	<u>o</u> -xylene
15 mm	30.7	8.1	---
760 mm	7.8	28.3	2.0

Under pyrolytic conditions, sulfones contained within already strained rings expand to form sulfinic acid intermediates. Dibenzothiophene-5,5-dioxide, 27, lost sulfur monoxide rather than sulfur dioxide at 690 degrees under a nitrogen atmosphere to yield dibenzofuran and dibenzothiophene.<sup>24</sup> Pyrolysis of 27 in the inlet tube of a mass spectrometer showed that the primary fragmentations of the parent ion were losses of SO or CO, requiring prior formation of a carbon-oxygen bond.<sup>24,25</sup> Pyrolysis of 28 under a nitrogen atmosphere at 400 degrees yielded 29 and 30 and a CO-CO<sub>2</sub> mixture.<sup>26</sup> Under the same conditions in the presence of 9,10-dihydroanthracene, 31, a sulfinic acid, was only isolated. This 31 had the same uv spectra as 28; its ir contained new bands at 1120 and 940 cm<sup>-1</sup> for the sulfinic acid group; and its nmr now exhibited non-equivalent methylene protons at  $\delta$  5.98 (the proton cis to the S=O group) and  $\delta$  5.31 with  $J_{AB} = 14$  Hz. Pure 31 pyrolyzed under the same conditions as 28 yielded the same ratio of 29:30 (1:3). Pyrolysis of 32 at 240 degrees yielded perylene and polymer while pyrolysis at 170 degrees afforded the sulfinic acid 33 in 54% yield.<sup>27</sup> No evidence for a sulfinic acid intermediate has ever been shown in a successful pyrolytic ring contraction.

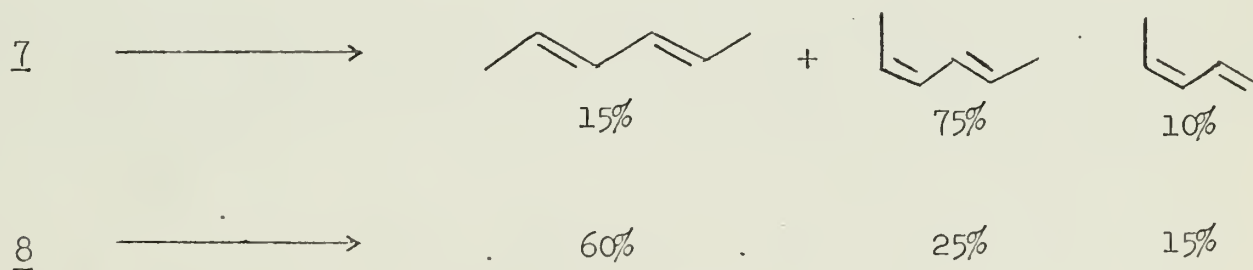






# PHOTOLYSIS

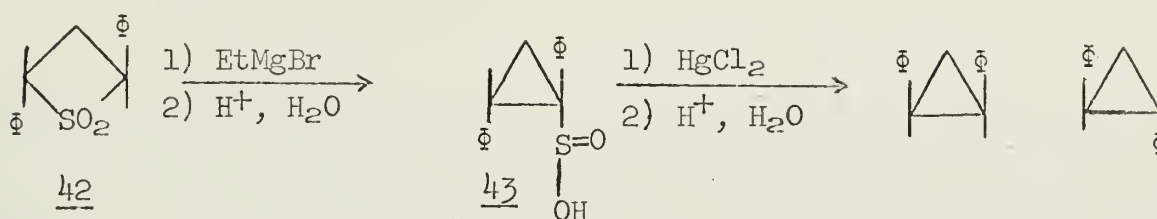
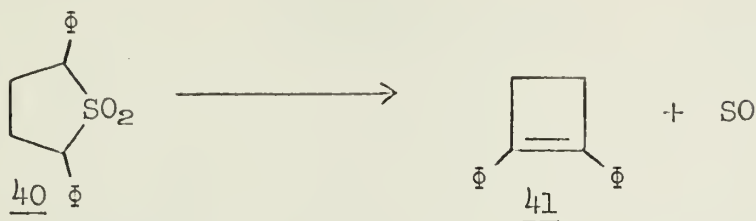
Photolytic loss of sulfur dioxide from 7 and 8 yields predominantly the olefins whose stereochemistry would be produced by a conrotatory mode of opening.<sup>28</sup> Initial fragmentation must then occur from an electronically excited state of the sulfone prior to crossing into the ground state of the products.



Photolytic ring closure has usually been attempted when it was thought the ring contracted compound was unstable to the extreme conditions of pyrolysis. Only two cases have been reported where ring contraction occurred: with the *cis-trans* mixtures of 34 and 35 producing the *trans*-diphenyl benzocyclobutene, 36; and *trans*-diphenyl naphtho[b]cyclobutene 37.<sup>29</sup> The unsubstituted 1 and 3, which are thermally the most stable and would produce less stable *o*-quinodimethanes than their phenyl substituted analogues, show no photochemical reaction in the cold even with high energy ultraviolet light (down to 220 nm) or with triplet sensitizers.

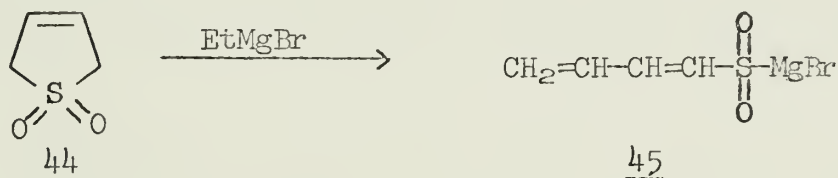


bromide in refluxing ether-benzene followed by work-up with acid, 42 yields the sulfinic acid 43. This 43 can be reacted with mercuric chloride to produce an organo-mercury compound which can be hydrolyzed to the cis/trans (0.125) mixture of 1,2-diphenylcyclopropanes.<sup>32</sup>

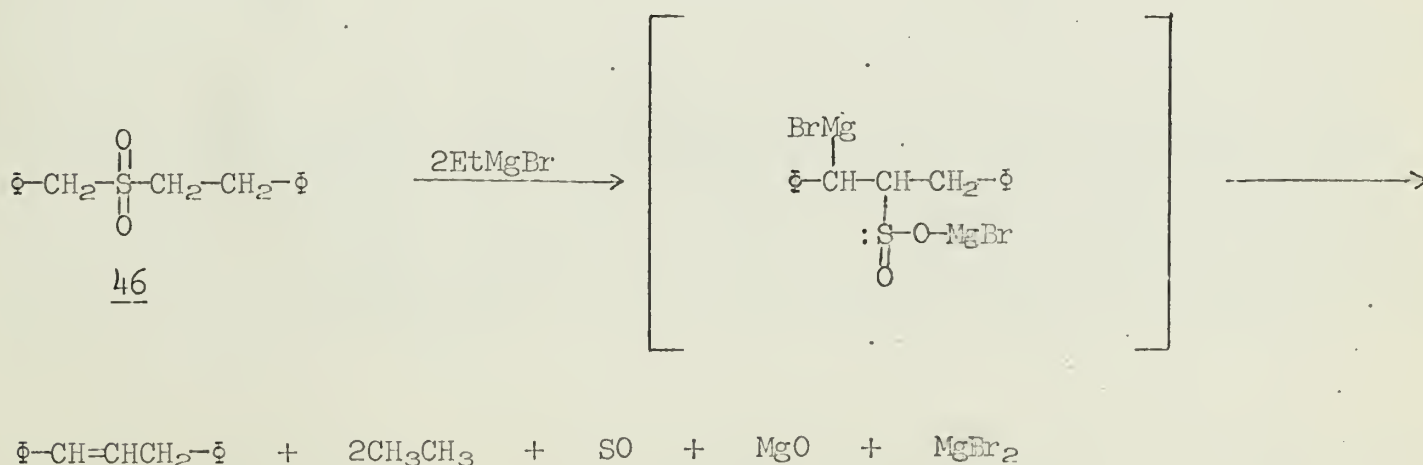


When 42 is refluxed with magnesium bromo *t*-butoxide, only the ring expanded sulfinate ester is isolated.<sup>33</sup> It is assumed that because of its steric bulk, *t*-butoxide cannot pull off an  $\alpha$  proton. All that can occur is a rearrangement caused by magnesium bromide coordinating with a sulfonyl oxygen and acting as an electron sink to break the sulfur-carbon bond.

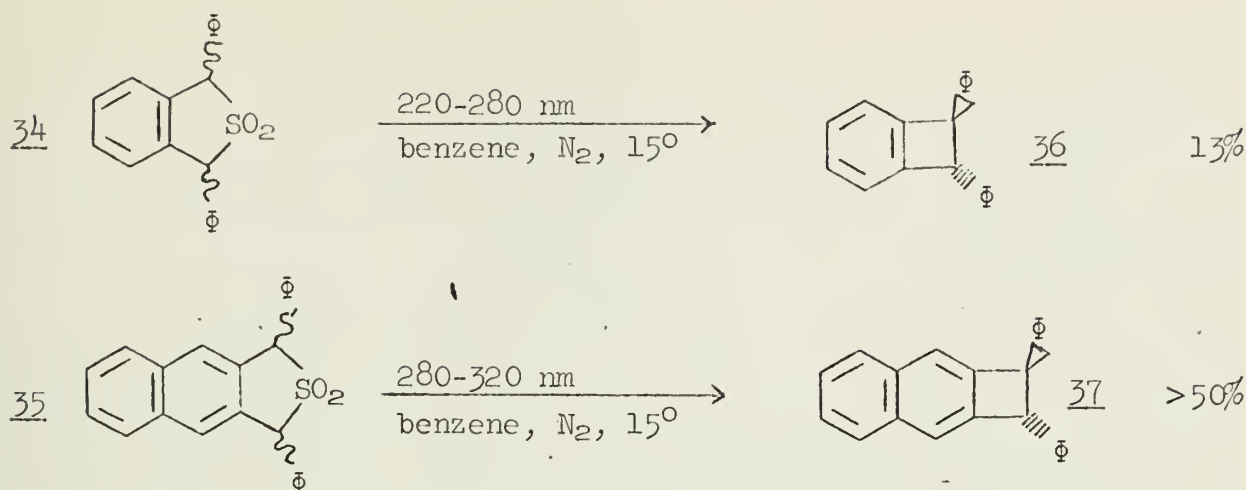
Reaction of 44 with ethyl magnesium bromide was accompanied by the evolution of ethane and the magnesium bromide salt of the sulfinic acid was isolated.<sup>34</sup> Upon acid hydrolysis, 45 yielded the free sulfinic acid.



The acidity of the  $\alpha$  protons of a sulfone toward Grignard reagents and the intermediate formation of a magnesium bromide salt of the sulfinic acid are used in the mechanism to explain olefin and sulfur monoxide production from linear 46 benzyl  $\beta$ -phenethyl sulfone.<sup>35</sup> And the analogous mechanism follows for ring contraction of 40.<sup>31</sup>

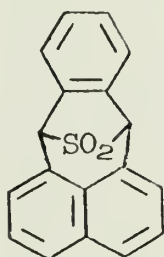




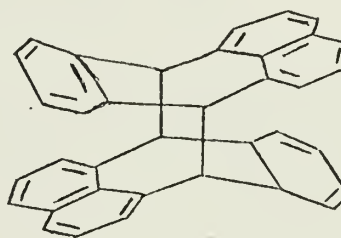


Ultraviolet assisted pyrolysis of 1 in the gas phase consistently gives higher total yields of products but the same molar ratio of ring contraction product to dimer ( $\frac{2}{25} = 4$ ) as the unassisted pyrolysis at the same temperature and pressure.<sup>23</sup> Irradiation accelerates the rate of desulfonylation while not affecting the fate of the reaction intermediate; and, since the product ratio ( $\frac{2}{25}$ ) remains equal to 4 for both the uv assisted and unassisted reactions throughout the temperature range of 200-300 degrees, the intermediate for both reactions must be the same 11.

Triplet sensitized photolysis of 38, 7,12-dihydropleiadene-7,12-sulfone, yields the same dimer 39 that is produced by pyrolysis.<sup>29</sup> The nmr of 39 shows a singlet for the four bridgehead hydrogens at  $\delta$  5.62 and proves the head-to-tail configuration by exhibiting naphthalene protons as low downfield as  $\delta$  7.7 (same as for acenaphthene) while also showing four para hydrogens on benzene at  $\delta$  6.77 (highly shielded by being placed above the center of the naphthalene rings).<sup>30</sup> It is suggested that the energy of the triplet state lies between 59.5 and 53.0 kcal/mole since, when using light of wavelength greater than 320 nm, no reaction



38



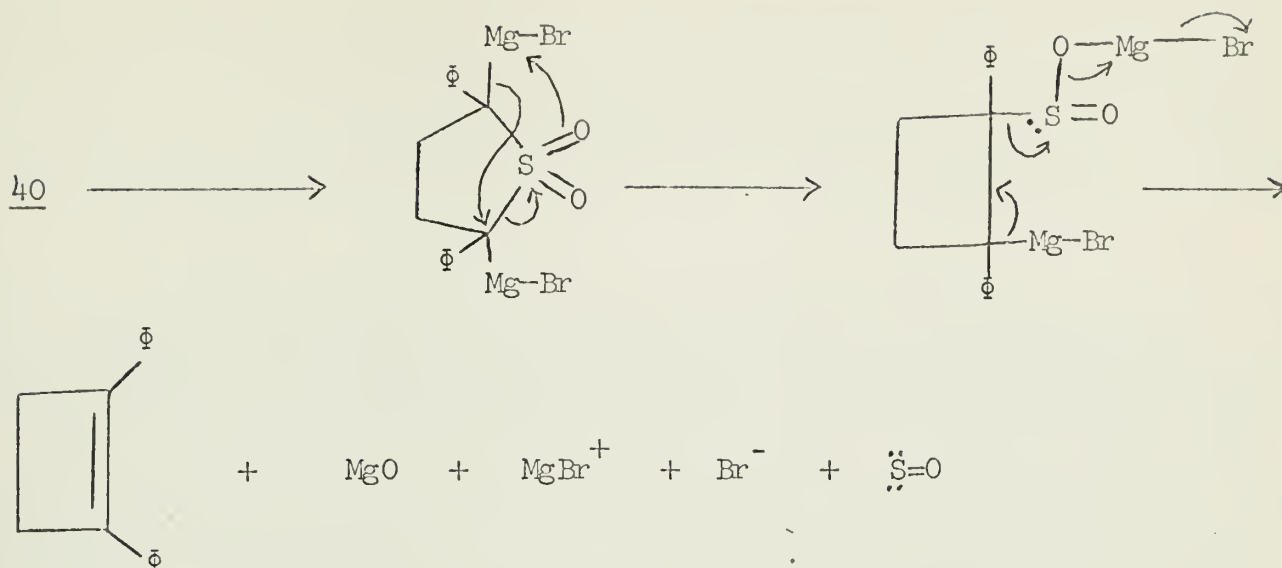
39

occurred with fluorenone as sensitizer but did when  $\beta$ -naphthaldehyde was used. Cava<sup>29</sup> believes that the sensitized reaction involves a naphthalene-like triplet with intersystem crossing to a highly vibrationally excited singlet ground state. This singlet then decays within the time order of diffusion control to yield sulfur dioxide and an o-quinoid pleiadene hydrocarbon. The o-quinoid cannot be trapped with N-phenyl maleimide under the conditions employed because the trapping reaction is slower than dimerization.

#### GRIGNARD REAGENTS

Reaction of 40 with ethyl magnesium bromide in ether-benzene gives 41 in 47% yield with apparent loss of sulfur monoxide.<sup>31</sup> When treated with ethyl magnesium





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January 5, 1970

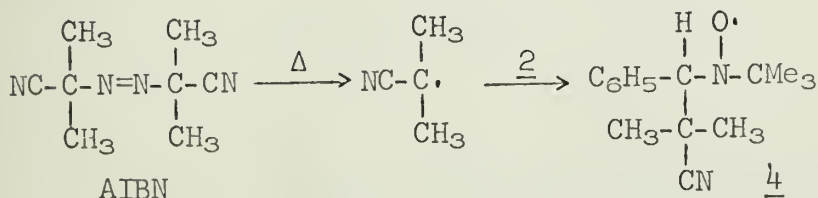
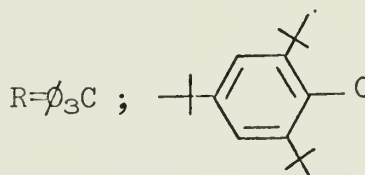
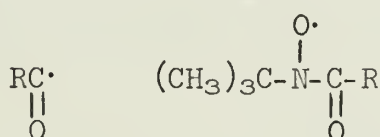
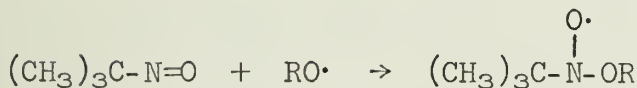
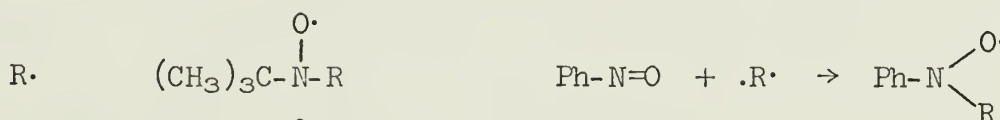
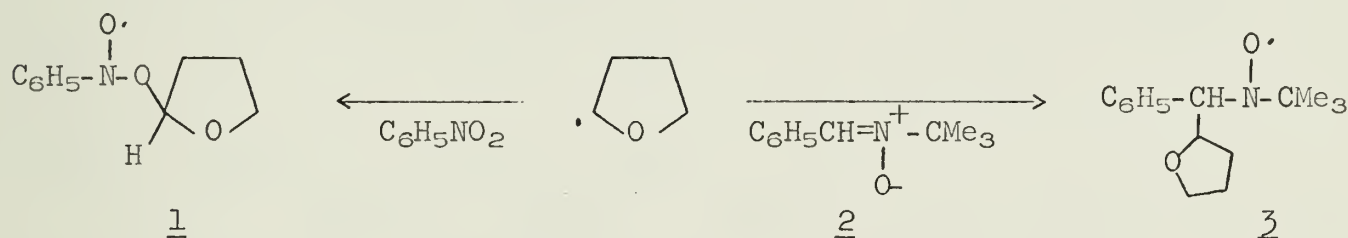
Nitroxide radicals (.... -N-oxyl), with the general formula  $R-\dot{N}-R'$ , where R, R' may be aryl or alkyl, are synthesized by a variety of routes. They are among the most stable radicals and their study has attracted both theoretically and synthetically oriented chemists. The chemistry of nitroxides and the earlier spin-labeling studies of protein and nucleic acids have been reviewed by Hamilton and McConnell.<sup>1</sup> This seminar will be primarily concerned with the studies directed toward their formation and applications.

## FORMATION

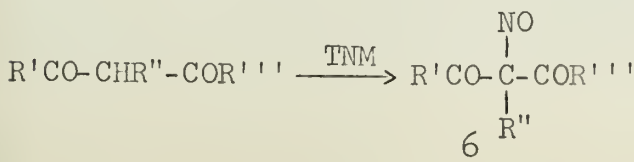
A variety of methods has been described in the literature for the formation of nitroxides. The main methods for the synthesis of radicals of this type are:

Addition of short-lived free radicals to nitro-, nitroso-, and nitrone compounds.

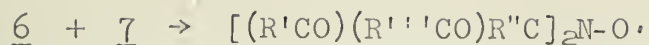
Janzen and Gerlock<sup>2</sup> reported that the photolysis of nitrobenzene in THF gave the structure 1 and in the presence of 0.1 M phenyl-t-butylnitron (2) the spin adduct 3 is obtained. The result suggests that the photolysis of nitrobenzene in THF does lead to the tetrahydrofuran radicals which react with the solvent or 2 to give the desired products. Nitrosoalkanes possess free-radical scavenging properties that react with alkyl,<sup>3,4</sup> or alkoxy<sup>5</sup> radicals to give stable, substituted nitroxides with characteristic esr spectra. The reaction of 2-nitroso-2-methylpropane with alkyl, aralkyl, alkoxy, and acyl radicals produces the corresponding t-butyl nitroxides.<sup>6</sup> Aromatic nitroso compounds are relatively easily accessible, Abakumov and Razuvaev<sup>7</sup> report that stable radicals e.g., triphenylmethyl and 2,4,6-tri-t-butylphenoxy react with nitrosobenzene in benzene solutions.



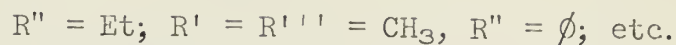
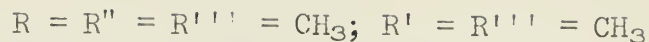
It has been found that AIBN reacts with 2 in xylene at 110° to give nitroxide 4.<sup>8</sup> The reaction<sup>9</sup> of 2-monosubstituted 1,3-dicarbonyl compounds, R'CO-CHR''-COR''', with tetranitromethane (TNM) produces symmetric nitroxides, [(R'CO)(R'''CO)R''C]<sub>2</sub>N-O (5). TNM is proposed to have a twofold action in the reaction leading to the symmetric nitroxides 5. It nitrosates the 1,3-dicarbonyl compound to give the nitroso compound 6 and oxidizes a second molecule to the radical 7 which is trapped by 6.



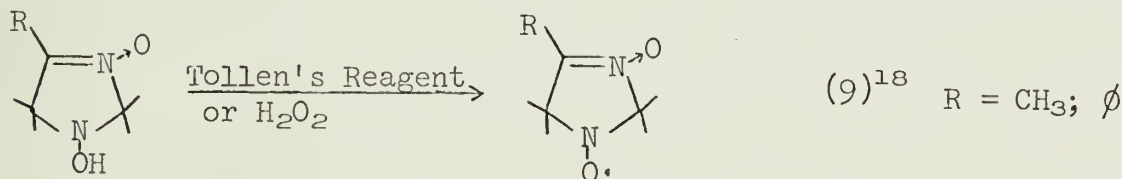
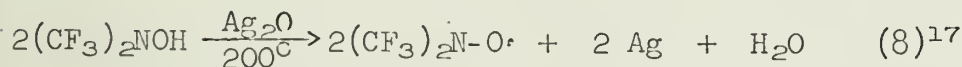
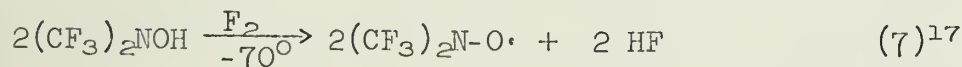
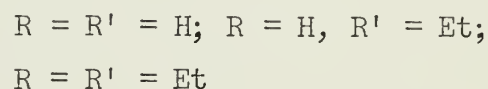
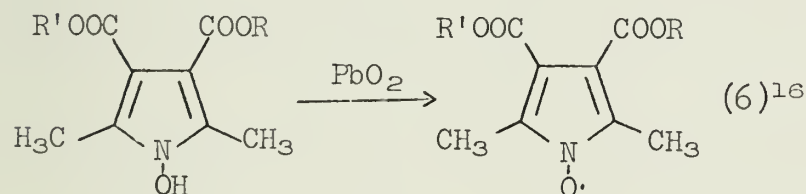
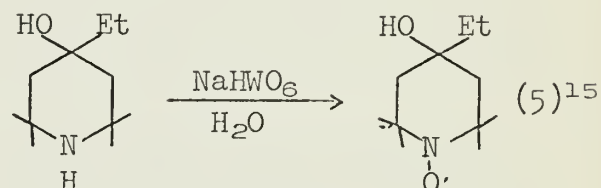
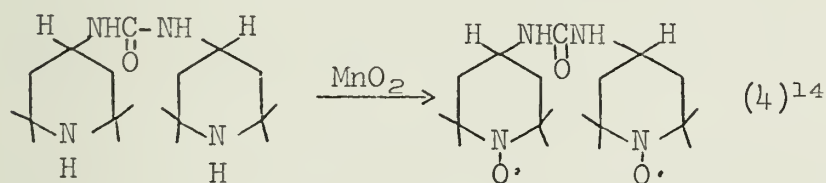
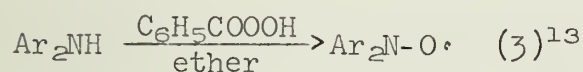
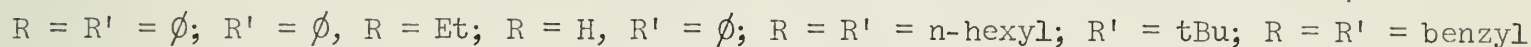
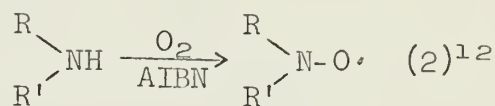
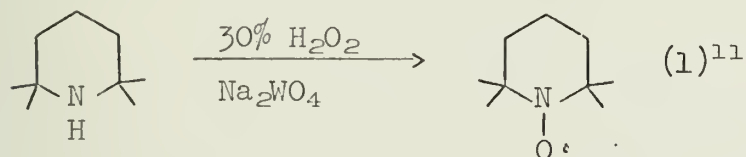




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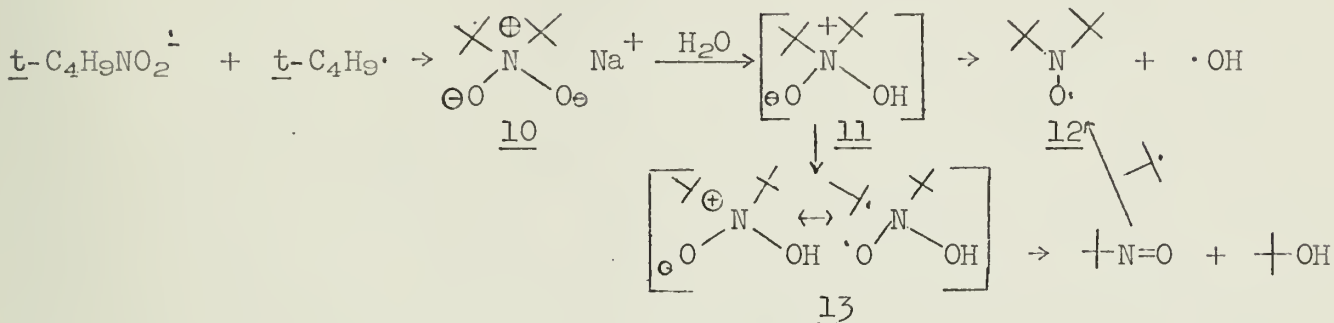
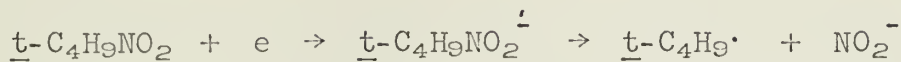
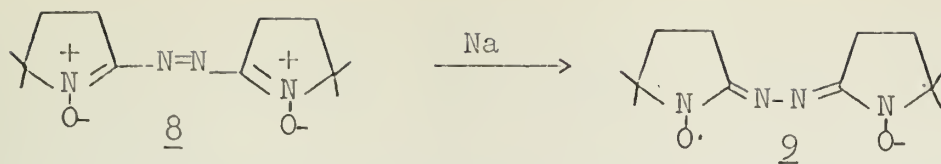


Oxidation of corresponding amines or hydroxyamines. A series of papers by Hudson and Hussuin have examined the use of hydrogen peroxide to oxidize amines to nitroxides.<sup>10</sup> Some other oxidizing agents which have been used are summarized in the following equations.



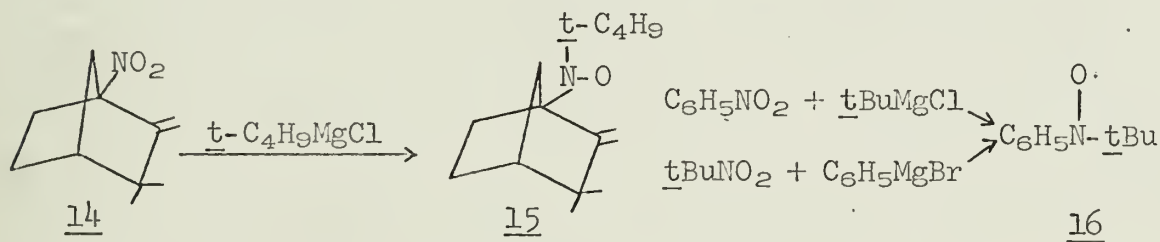
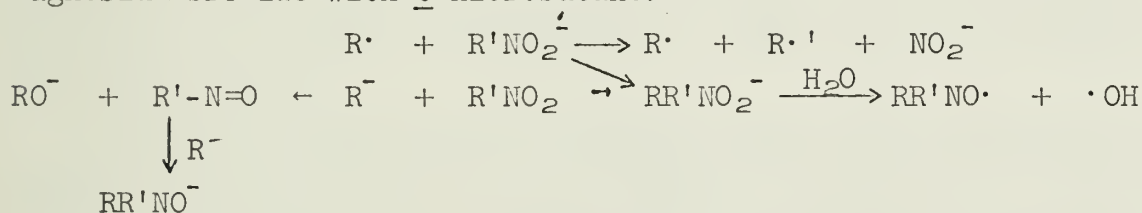
Reduction of nitro-, or binitrone compounds with alkali metal. Forrester et al.<sup>19</sup> reported that reduction of azo-1-pyrroline-1-oxide (8) with sodium gives the blue nitroxide radical anion 9. Hoffman and his coworkers<sup>3</sup> have studied the reaction of sodium with t-nitrobutane in 1,2-dimethoxyethane. The formation of di-t-butylnitroxide involves the reaction of a t-butyl radical, derived from the fragmentations of a t-butylnitro anion radical, with additional t-butylnitro anion radical to form a diamagnetic salt 10,  $(t-C_4H_9)_2NO_2 Na^+$ . Its structure is supported by an independent synthesis of an analogous compound. This salt upon hydrolysis gives an intermediate 11 which decomposes to give nitroxide 12 and a hydroxy radical. However, the decomposition of 11 by another route is plausible involving an ion-pair or radical-pair intermediate 13.





Reaction of organometallics with nitro compound. On the basis of evidence that hydrolysis of 10 gave nitroxide 12, Hoffman and his coworkers<sup>20</sup> found a convenient route to nitroxides in the reaction of organometallics with nitro compounds. The attack of carbanions on nitro compounds may take one of several routes. Attack may occur directly at the nitrogen atom of the nitro group to give an intermediate (presumed to be a hydroxylamine oxide salt) which on hydrolysis affords nitroxides. The carbanion may also reduce the nitro compound to its anion radical or it may attack at the oxygen atoms of the nitro group.

The reaction of *t*-butyl magnesium chloride with nitro-1-camphene (14) in ether, followed by reaction with ammonium chloride solution, ether extraction, evaporation, yields the nitroxide 15.<sup>21</sup> Similarly, phenyl *t*-butyl nitroxide (16) can be obtained by the reaction of either *t*-butyl magnesium chloride with nitrobenzene, or of phenyl magnesium bromide with *t*-nitrobutane.<sup>22</sup>



## ESR OF NITROXIDE RADICALS

The approximate spin Hamiltonian,  $\hat{H}$ , for a free radical is  $\hat{H} = g\beta\vec{S}\cdot\vec{H} + a\vec{S}\cdot\vec{I} + [\text{electron-electron dipole}] + [\text{electron-electron exchange}]$  where  $\beta$ ,  $H$ ,  $g$ ,  $a$ ,  $S$ , and  $I$  are terms

are the electron Bohr magneton, the magnetic field, the spectroscopic splitting factor, the hyperfine coupling constant, the electron spin operator, and the nuclear spin operator, respectively. The nuclear Zeeman term has been omitted and small second-order effects are not discussed here. The first term in  $\hat{H}$  is the electron Zeeman term and represents the interaction of the electron spin with the external magnetic field. This large interaction gives rise to the useful relation  $h\nu = g\beta H$  where  $\nu$  (in KMHz) is the microwave frequency of the esr spectrometer. The second term in  $\hat{H}$  represents the interaction between the unpaired electron and the nitrogen nucleus



of the nitroxide N-O group. This term, although much weaker than the Zeeman interaction, yields the important rule that a nuclear spin,  $I$ , will split the single Zeeman line into  $2I+1$  lines. For nitrogen,  $I = 1$ , and the result is three lines of equal intensity.

The appearance of the esr spectrum can be characterized by the line width and two important parameters, the  $g$  value and the coupling constant,  $a$ . The  $g$  value determines the center of the spectrum, and  $a$  is simply the distance between the two hyperfine splitting lines. Increasing or decreasing  $g$  will shift the entire spectrum to lower or higher magnetic fields, respectively, without altering the distance between the hyperfine splitting lines. Similarly, variations in  $a$  expand or contract the pattern without altering the position of the center line. Usually, esr spectroscopists prefer to describe changes in resonance frequency by saying that the effective magnetic moment of an electron ( $\mu_e = -g\beta S$ ) can be different in different situations, so that the value of  $g$  is not constant. When the unpaired electron is placed in a different chemical environments, the orbital motion of the electron is perturbed differently. Also, the unpaired electron has orbital angular momentum which will couple to the spin angular momentum, a net orbital magnetic moment will result. It will give rise to a change in  $g$  value. In most free radicals the spin-orbital coupling is small, the  $g$  values are nearly equal to the free electron value of 2.0023. The small deviations (0.05 or smaller) observed for most nitroxide radicals in different solvent system are accounted for by changing the spin densities on nitrogen and oxygen which are related to the energy difference between the odd-electron orbital and lone-pair electron orbital. In general the magnitude of  $g$  depends on the orientation of the nitroxide molecule with respect to the magnetic field. In a solution or in the gas phase,  $g$  is averaged over all orientations because the nitroxide molecules are tumbling rapidly and randomly. In solid state studies the crystal can be rotated to align the magnetic field with the x, y, and z axes of the oriented nitroxides, giving different  $g$  values for each orientation. The same considerations are true for the hyperfine coupling constant  $a$ . The anisotropy of  $a$  and  $g$  parameters is important for spin-labeling study because it can be used directly to serve the orientations of spin labels in crystals and membranes or other biological structures.

#### SPIN LABEL STUDIES

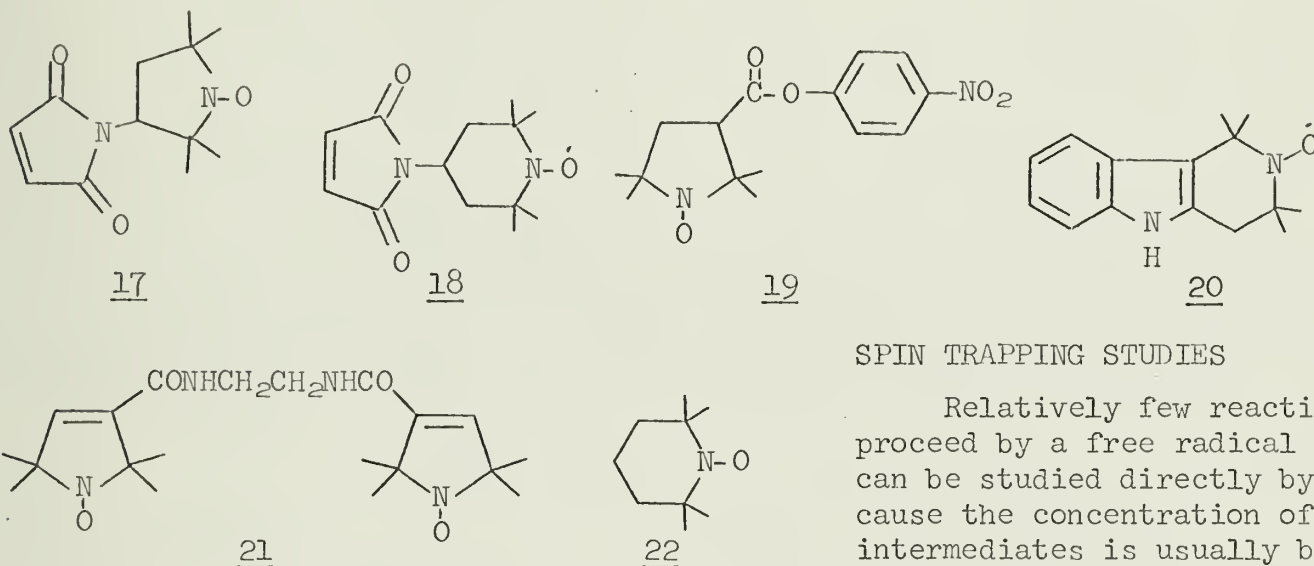
The first description of a labeling study using nitroxides was reported in 1965 by Stone, et al.<sup>24</sup> Recently, a comprehensive survey of spin labeling was done by Griffith and Waggoner.<sup>25</sup> The spin labeling technique is a useful tool for studying the chemistry, structure and dynamics of biological macromolecules such as proteins and nucleic acids. The technique consists of chemically bonding a paramagnetic molecule (the spin label) to a macromolecule that is not ordinarily paramagnetic. The resulting compound gives an esr spectrum. The method is highly selective, both spectrally and chemically. Specific sites on a macromolecule can be tagged by choosing the appropriate spin label and reaction condition. One of the beauties of the technique is that in many cases we can tailor-make a spin label to tie to a specific part of the macromolecule we want to study.

Nitroxides whose nitrogen atom is bonded to a tertiary carbon are excellent spin-labeling compounds. They are stable under a wide range of conditions and are soluble in polar and nonpolar solvents. In addition their simple esr spectra are sensitive to molecular motion because both  $a$  and  $g$  are anisotropic.

Some of the spin labels McConnell<sup>26</sup> used have a five or six-membered ring structure. Attachment to a macromolecule is through a functional group on the spin label. Bonding can be either covalent or hydrophobic. Labels 17 and 18 form covalent bonds to sulfhydryl groups in proteins such as hemoglobin and serum albumin. Label 19 acylates the serine residue at  $\alpha$ -chymotrypsin's active site. Label 20 bonds hydrophobically to a nicotinamide adenine dinucleotide site in alcohol dehydrogenase. This is analogous to fluorescent dyes that bind to proteins in their hydrophobic regions.



A spin label, bound to a macromolecule, exhibits resonance spectra that can range from "strongly immobilized" to "weakly immobilized" depending on its rotational freedom relative to the macromolecule. The more rigid the connection, the stronger is the degree of immobilization. By observing whether spin immobilization is strong, intermediate, or weak, we can deduce something of the macromolecule's architecture. Recently Calvin et al.<sup>27</sup> have explored the behavior of pair interaction in biradical 21 when it is bound by van der Waal's forces in a lobster nerve membrane. The esr spectrum of 21 was markedly changed upon contact with nerve and suggested that the biradical molecule is bound to some part of the membrane (probably lipid). Hubbell and McConnell<sup>28</sup> allowed nitroxide 22 to diffuse into several membranous system and used esr spectra to show the existence of hydrophobic regions in the membranes.



#### SPIN TRAPPING STUDIES

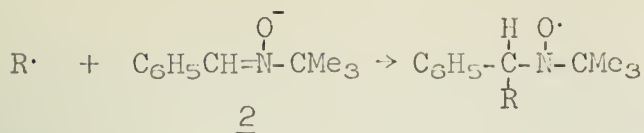
Relatively few reactions which proceed by a free radical mechanism can be studied directly by esr, because the concentration of radical intermediates is usually below the detection limit of commonly used

spectrometers. Hence spin trapping techniques are needed to detect and identify the short-lived radicals, e.g. methyl, *t*-butoxy, vinyl radicals, in the reacting system. Recently several reports have appeared on esr studies of addition reactions which have been mentioned in the formation section. The short-lived radicals are trapped by nitro, nitroso, and nitron functions to produce the stable nitroxides.

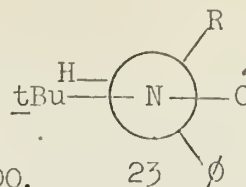
Photolysis of alkyl nitrites in hydrocarbon solvents gives dialkyl nitroxides and alkoxy-alkyl nitroxides.<sup>6</sup> However, Shih et al.<sup>29</sup> have used different solvents to study the reactions which occur in these systems. Lagercrantz and Forshult<sup>30</sup> trapped radiation-produced free radicals by dissolving irradiated solids in a solution of nitroso-*t*-butane and Chalfont, et al.<sup>31</sup> detected a substituted *t*-butyl nitroxide in *t*-butoxy-initiated styrene polymerization. Janzen and Blackburn<sup>32</sup> have shown that photolysis of organolead, -tin, and -mercury compounds trapped by 2 to obtain the radical addition products,  $\alpha$ -substituted benzyl-*t*-butyl nitroxides, which are verified by the nitrogen and  $\beta$ -hydrogen hyperfine coupling constants. Also, they have reported the feasibility of using 2 as a free-radical trap to detect and identify short-lived radicals.<sup>33,34</sup> Information useful in defining the structure of the trapped radical lies in the magnitude of the  $\beta$ -H and nitrogen hfc's. The  $\beta$ -H hfc depends on the dihedral angle which in turn depends on the bulk of R. It can be seen from the projection diagram of conformation 23 that when R is phenyl the dihedral angle is nearly zero i.e. the  $\beta$ -H hfc is smallest. The magnitude of the  $\beta$ -H hfc increases when the bulk in R is either larger or smaller than phenyl. The correlation is not perfect, however, since the value of the  $\beta$ -H is also dependent on the electronegativity of R. The N hfc is also sensitive to the electronegativity of R, inductive electron withdrawal producing a smaller N hfc. During the investigation on the mechanism of oxidation with nickel peroxide,<sup>35</sup> nitrosobenzene and 2-methyl-2-nitrosopropane have been used as radical traps to detect the short-lived radical intermediates as nitroxides (spin adducts). The characterization of the nitroxides was through the esr spectra.

Spin trapping techniques have been applied for the detection of free radicals in the many other reactions involving e.g., radiation damage<sup>30</sup> and polymerization.<sup>31</sup>





R = C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, CF<sub>3</sub>, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, n-C<sub>4</sub>H<sub>9</sub>, CH<sub>3</sub>COO, C<sub>6</sub>H<sub>5</sub>COO.



## SUBSTITUENT EFFECTS ON ESR SPECTRA

Esr spectroscopy offers a convenient method for measuring substituent effects on electron density. The hfc of a nucleus is related to unpaired electron density. Since the Hammett  $\sigma$  Constant is interpreted as a measure of the substituent effect on electron density on the atom,<sup>36</sup> the substituent effect on nuclear hfc in aromatic free radicals might be expected to relate in some manner to appropriate  $\sigma$  constants. Numerous studies of substituent effects on the esr spectra of nitroxides have been reported and have been reviewed by Janzen.<sup>37</sup> The N hfc's in diphenyl-, t-alkenyl-phenyl-, t-butylphenyl-, phenylhydro-, and phenylbenzoylnitroxides can all be correlated by  $\sigma$  in the Hammett equation. A plot of N hfc and H hfc in substituted phenylhydronitroxides vs  $\sigma$  and  $\sigma^-$  is shown in Fig. 1. The slopes of the two lines are the same. Since the hfc values depend primarily on the spin density on nitrogen,<sup>38</sup> the spin density must follow the Hammett equation. The nitroxide function is sensitive to the polar effect of substituents. The nitroxide bond is a three- $\pi$ -electron two atom function wherein resonance structure 24 is favored when the substituent is electron withdrawing (which causes a decrease in the N hfc) and 25 is favored when the substituent is electron donating (which causes an increase in the N hfc).

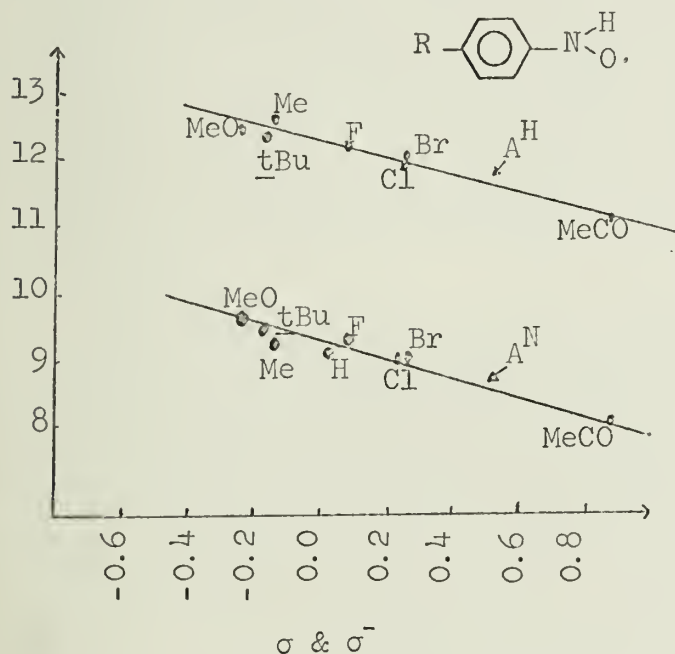


Fig. 1. Plots of N hfc and H hfc in p-substituted phenylhydronitroxide vs  $\sigma$  and  $\sigma^-$ .

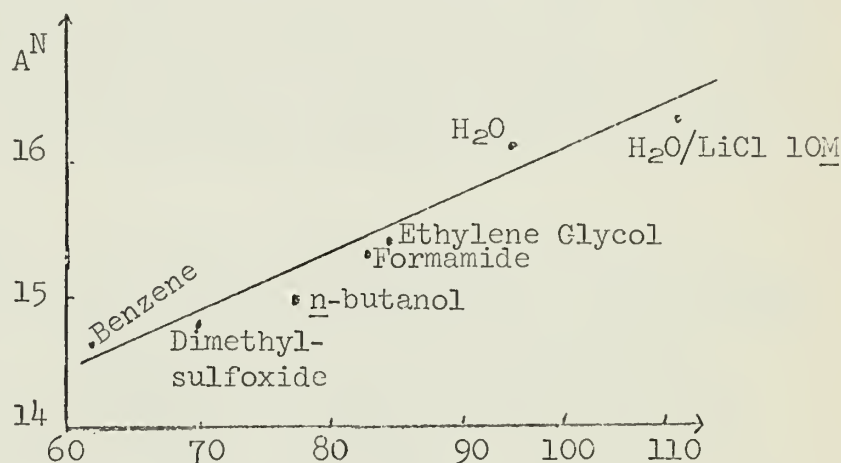
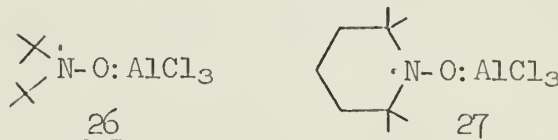
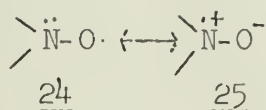


Fig. 2. Dependence of N hfc on Kosower's Z factor for various kinds of solvent.



## SOLVENT EFFECTS ON ESR SPECTRA

During the study of esr hyperfine spectra of diphenylnitroxide, Deguchi<sup>39</sup> found that the values of N hfc and H hfc vary from one solvent to the other. The N hfc is approximately linearly proportional to the dielectric constants of the solvents. However, Rassat et al.<sup>40</sup> reported that the N hfc of nitroxide 22 is varied linearly



with Kosower's Z factor as shown in Fig. 2. More polar solvents favor resonance structure from 25 and this increases the N hfc value.

The  $g$  value is also solvent dependent. Kawamura et al.<sup>41</sup> reported that the  $g$  values of 12 are shifted in the various solvents. The  $g$  values were decreased in the hydrogen bonding solvents. When aprotic solvents are employed, a change in the odd-electron orbital and a lowering of the lone-pair orbital energy take place; when protic solvents are used, the odd-electron orbital also changes, but a more remarkable lowering of the lone-pair orbital energy due to hydrogen bonding. The  $g$  value of this radical is given by Stone<sup>23</sup>,  $g = 2.00232 + \Delta g$ . The  $\Delta g$  is inversely proportional to the energy difference between the lone-pair orbital and the odd-electron orbital.

#### FREE RADICAL MOLECULAR COMPLEXES

Recently, Hoffman and Eames<sup>42</sup> found that nitroxide 22 can be protonated by a Brønsted acid (a strong Lewis acid coordinated with residual water in an organic solvent). These protonated species contain a nitroxide which is bonded through a lone pair of electrons but still retains its unpaired electron. These species exhibit six-line spectra in which each of the three  $^{14}\text{N}$  lines is split into a doublet by interaction with the additional proton. Similarly, they<sup>43</sup> have discovered that aliphatic nitroxides form monomeric molecular complexes with strong Lewis acids. These complexes are stable in solution and demonstrated well-resolved hyperfine interactions with the nucleus of the acid as well as with nuclei of the nitroxides. The paramagnetism of these complexes offers a new technique for studying the nature of Lewis acid-base interactions. The complexes of nitroxides 12 and 22 with aluminum chloride, 26 and 27, exhibit 18-line spectra in which each of the three  $^{14}\text{N}$  lines is split into six by interaction with a single  $^{27}\text{Al}$  ( $I = 5/2$ ) nucleus. Upon complexation the  $^{14}\text{N}$  hfc of the parent nitroxides increases and the  $g$  values decreases. The N hfc increases can again be explained by reference to 25. Changes in the N hfc for a given nitroxide complexed with different acids will reflect the actual electronic structure within the adducts. The increase in the energy difference between the odd-electron orbital and the lone-pair orbital are mainly responsible for the decrease in  $g$  value.

#### NMR STUDIES

Nmr spectra of concentrated solutions of organic radicals have recently been reported.<sup>44</sup> In concentrated radical solutions, electron exchange may be rapid enough so that the nmr line could be observed. In cases where the radicals have moderate or poor solubility, at intermediate rates of exchange, one gets line broadening and spectra can not be observed. The lines from protons with large coupling constants which would require larger rates of electron exchange, are generally impossible to detect. Kreilick<sup>45</sup> has conducted experiments in which the liquid free radical di-*t*-butylnitroxide (12) was used as a solvent (spin relaxer) for a second radical. Spin exchange between the solvent and solute molecules rapidly averages the electron spin levels of the solute molecules, and the nmr spectrum of many organic radicals in dilute solution is rendered observable. The lines from protons with relatively large coupling constants are also observable. The unpaired electrons change the magnetic field experienced by the magnetic nucleus. This causes a very large chemical shift of the lines in the nmr spectrum which is known as a contact shift. For example, the nmr shifts and the calculated electron spin-nuclear spin coupling constants of the phenoxy radical 28 are given in Table 1.<sup>45</sup>

The direction and magnitude of these shifts can be used to determine the sign and magnitude of the coupling constants. The coupling constant and the shift,  $\Delta H$  are related by  $\frac{\Delta H}{H} = \frac{\Delta \nu}{\nu} = -a_i \left( \frac{\gamma_e}{\gamma_N} \right) \frac{g\beta}{4kT}$  where  $\gamma_e$  is the magnetogyric ratio for the electron,

$\gamma_N$  is the magnetogyric ratio for the magnetic nucleus. These nmr spectra are particularly useful in determining small coupling constants which are below the limit of resolvability of esr. Also analysis of the nmr spectra is much simpler than analysis of the esr spectra.



Table 1. Shifts and Coupling Constants for the Various Protons in Radical 28

Proton	Shift, <sup>a</sup> kHz	a <sub>i</sub> , G
Phenoxy ring protons	-13.75	+1.85
Methoxy protons, <u>anti</u>	- 6.09	+0.82
Methoxy protons, <u>syn</u>	- 2.90	+0.39
t-Butyl protons	- 0.54	+0.074
α-Cyclopropyl proton, <u>anti</u>	+14.98	-2.02
α-Cyclopropyl proton, <u>syn</u>	+ 5.43	-0.73

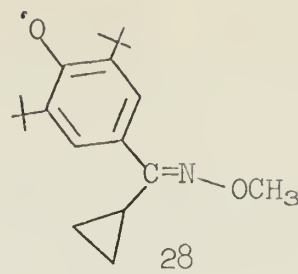
<sup>a</sup> The shifts are from the corresponding peak in the spectrum of the diamagnetic phenol. <sup>b</sup> The four methylene protons on the cyclopropyl ring may be hidden under another peak.

## CONCLUSION

Nitroxides, with their stable and characteristic paramagnetic nucleus, are uniquely valuable organic radicals for mechanistic studies of reactions involving free radical intermediates or for probing biomolecular structures.

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## SYNTHESIS VIA HYDROBORATION

Reported by Richard B. Chapas

January 8, 1970

## INTRODUCTION

Since Brown's comprehensive summary<sup>1</sup> of the hydroboration process, a phenomenal amount of work has been done in this area. More recently, a review of the reaction of organoboranes with carbon monoxide has been published;<sup>2</sup> other partial summaries are available.<sup>3-5</sup> However, there has been no recent comprehensive review of the application of hydroboration to organic synthesis.

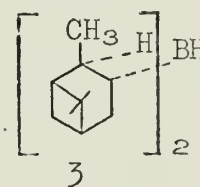
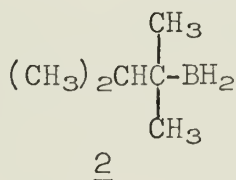
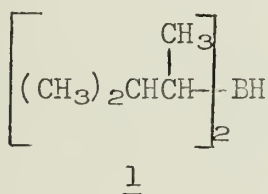
Although a considerable amount of research has been directed toward the kinetic and mechanistic aspects of this process, the primary concern of this review is the synthetic application of hydroboration in organic chemistry. An attempt will be made to list the reactions according to similarity in mechanism and according to the various functional groups which can be introduced.

The great importance of hydroboration as a synthetic tool is easily seen in the availability of the starting materials and the mild reaction conditions. In most cases, alkenes are easily obtainable and inexpensive; diborane can be purchased commercially as a tetrahydrofuran solution or can conveniently be synthesized. Most reactions proceed rapidly at 0° and are complete in one or two hours. Isolation of the intermediate organoborane is usually disadvantageous.

The reaction of the hydroborating agent, usually abbreviated HB, and the alkene is a regiospecific<sup>6</sup> and stereospecific addition. Regiospecific is a word coined by Hassner to denote specificity in orientation or direction. Thus in the hydroboration reaction, a cis, anti-Markovinkoff addition results, which is highly sensitive to the stereochemical environment. Most reactions of the resulting organoboranes proceed with retention of configuration. In this way hydroboration can be used to obtain a stereospecific product.

## HYDROBORATING AGENTS

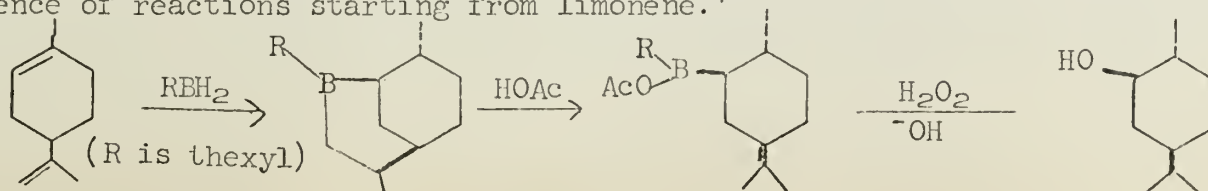
The specificity of the addition reaction is highly dependent on the hydroborating agent. Since the discovery of the hydroboration reaction, various other hydroborating agents have been used. Among those summarized by Brown<sup>1</sup> are (1) disiamylborane (di-s-isoamylborane); (2) thexylborane (t-hexylborane); and (3) diisopinocampheylborane. These are readily prepared by the controlled addition of diborane to the corresponding alkenes: 2-methyl-2-butene, 2,3-dimethyl-2-butene, and  $\alpha$ -pinene, respectively. The



advantage in the use of these organoboranes instead of diborane itself is that, where diborane gives 6% or more of the isomeric product, usually less than 2% is obtained with these more sterically hindered dialkylboranes. Thus hydroboration of styrene with diborane yields 80% of the terminal isomer and 20% of the nonterminal isomer; with disiamylborane, the yields are 98 and 2%, respectively.<sup>1</sup>

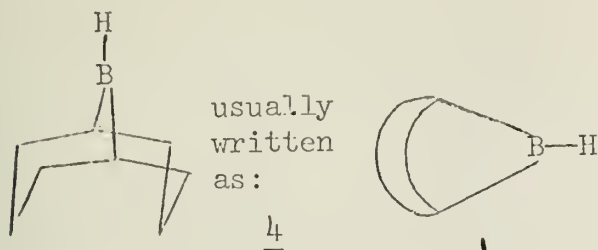
The use of diisopinocampheylborane offers a further advantage in synthetic work. Since  $\alpha$ -pinene is available in optically active form, the reaction of this olefin with diborane yields an optically active dialkylborane which exhibits a remarkable ability to achieve the asymmetric hydroboration of suitable olefins. Thus, by combining hydroboration with oxidation or amination, the synthesis of optically active alcohols and amines can be realized.

Thexylborane converts suitable diolefins cleanly to cyclic boranes. This is a useful tool for the stereospecific synthesis of alcohols, as illustrated by the sequence of reactions starting from limonene.<sup>7</sup>





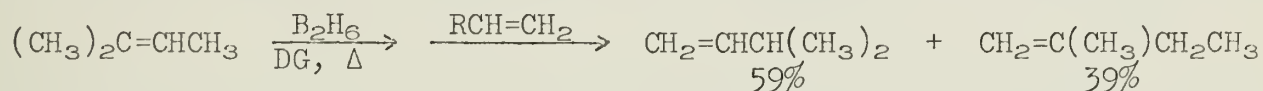
The alkylboranes listed have two major disadvantages. They are less reactive than diborane and can only be stored for limited periods. A new hydroborating agent, 9-borabicyclo[3.3.1]nonane (4), eliminates both these disadvantages, while still retaining the selectivity. This organoborane, abbreviated 9-BBN and drawn as indicated, is obtained from the reaction of 1,5-cyclooctadiene with borane in tetrahydrofuran.<sup>8</sup> It is remarkably stable, being inert toward atmospheric oxygen and remaining unchanged after 24 hours at 200°. Also the bicyclic reagent is much more reactive than disiamylborane and hydroborates unhindered olefins within a few minutes at 25°.<sup>9</sup>



#### CONTRATHERMODYNAMIC ISOMERIZATION

It has been found that organoboranes undergo a facile isomerization which places the boron atom at the least hindered position of the alkyl group. Further, by the use of a more reactive olefin or one equally reactive, but in high concentration, it is possible to displace the original olefin. Thus by a combination of these two processes, the contrathermodynamic isomerization of olefins can be achieved.<sup>1</sup>

Studies have been done on acyclic<sup>10,11</sup> and cyclic systems.<sup>12,13</sup> The presence of excess diborane is essential to the migration reaction. Further a quaternary carbon totally prohibits migration, while a single branch can be easily tolerated. The reaction is usually run in refluxing diglyme and is complete in two to four hours. For acyclic, non-aromatic systems, yields are usually 98% or better; however, both 1-alkenes are obtained, if two are possible, with the least hindered being favored. This is illustrated with 2-methyl-2-butene.<sup>10</sup> Less success is seen with



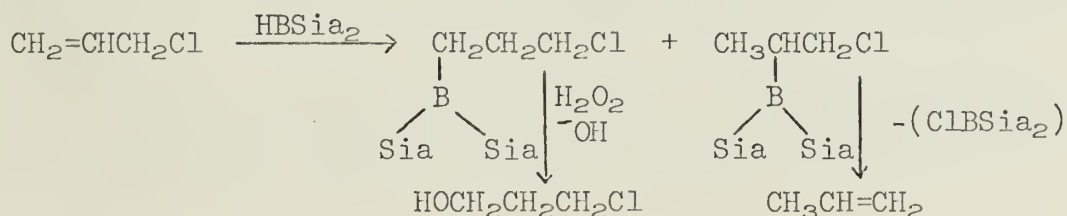
aromatic and endocyclic alkenes; 1-phenylpropene is isomerized to 3-phenylpropene in 78% yield and 1-ethylcyclohexene to vinylcyclohexane in 62% yield.

In the terpene series, the conversion of  $\alpha$ -pinene to  $\beta$ -pinene of high optical purity has been achieved.<sup>10</sup> Hydroboration of cholest-5-ene followed by refluxing in diglyme caused migration of the boron from the B ring to the A ring of the steroid, giving a mixture of products.<sup>14</sup>

#### OXIDATION

Upon treatment with alkaline hydrogen peroxide, organoboranes yield alcohols in high yield. Thus olefins can conveniently be converted to alcohols by hydroboration-oxidation. Wide variations in the structure of the olefin can be tolerated; thus highly hindered organoboranes, such as those obtained from norbornene and  $\alpha$ -pinene, react quantitatively. A further advantage is that the reaction is compatible with many other functional groups.<sup>1</sup>

The convenience and the essentially quantitative yields obtained have stimulated its use in the study of directive effects of various substituents on the hydroboration reaction; both cyclic and acyclic systems have been studied.<sup>15-22</sup> Among the substituents studied were the chlorides, hydroxide, ethers, and sulfonates. When these



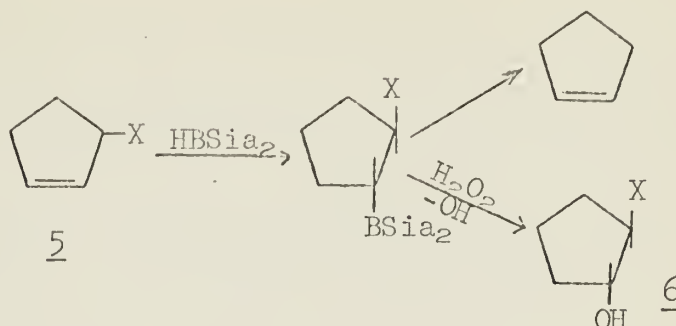
are placed in the allylic position, the result is a marked increase in substitution at the adjacent carbon which causes a spontaneous elimination for the chloro and acetoxy group. The use of disiamylborane ( $\text{HBSia}_2$ ) decreases the amount of addition at the adjacent carbon and allows the reaction to proceed in the normal manner.



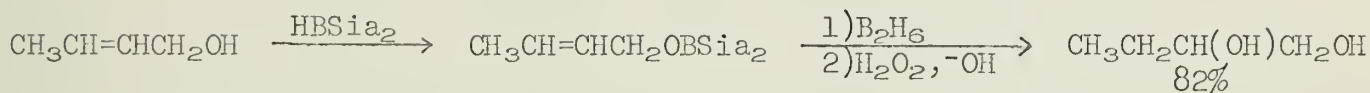
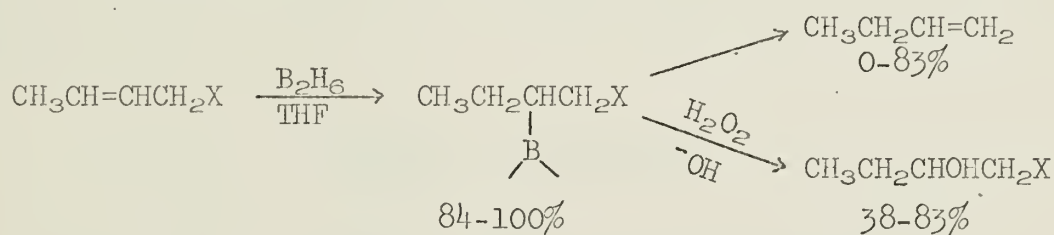
The directive effect of these substituents on hydroboration is seen more clearly in the 3-cyclopentyl system, in which 83-100% of the addition occurs at the adjacent carbon.<sup>21</sup> The results are summarized in Table I. A similar study was

Table I. Yields of Cyclopentyl Derivatives

<u>5</u>	% <u>6</u>	% Elimination
Chloride	0	87
Acetate	50	26
Ethyl Ether	66	7
Alcohol	80	8



performed on 2-butenyl derivatives.<sup>19</sup> Although the acetate and chloride eliminated spontaneously, the 1,2-product could be isolated with the other substituents. Glycols could thus be synthesized; higher yields were obtained if the alcohol or ketone was first converted to the disiamylborinate ester.



Hydroboration of 1-butenyl and related vinyl derivatives (chloro, acetoxy, ethoxy) gives complicated results in the case of the chloro and acetoxy group with the predominant reaction being  $\alpha$ -addition. However, with the ethoxy group,  $\beta$ -addition results and the 1-ethoxy-2-hydroxy derivative can be isolated in 80-94% yields.

The hydroboration-oxidation reaction has been carried out in the presence of many other functional groups. In the presence of an ester group, a 70% yield was obtained.<sup>23</sup> A study done on isophorone and 3-methylcyclohexenone, both conjugated ketones, yielded single diols.<sup>24,25</sup> In the presence of a carbamate, an 85% yield of the alcohol was obtained.<sup>26</sup> Hydroboration-oxidation of the morpholine or pyrrolidine enamine of 2-methylcyclohexanone gave the *trans*- $\beta$ -aminocyclohexanols in 80% yield.<sup>27</sup> The synthesis of *cis*- and *trans*-2-trimethylsilylcyclohexanol was accomplished in low yields by this method.<sup>28</sup>

By the hydroboration-oxidation reaction it is possible to obtain systems not readily available by other means. Thus *trans,trans*-2,5-di-*t*-butylcyclohexanol can be synthesized in 65% yield from 2,5-di-*t*-butylcyclohexene; the product is in the form of a twisted boat.<sup>29</sup>

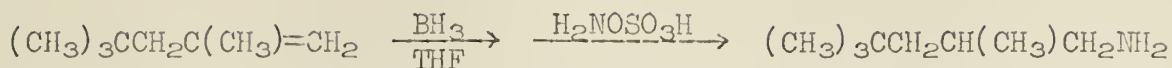
Numerous studies have been undertaken on families of compounds of biological interest, particularly in the alkaloid,<sup>30</sup> steroid,<sup>31</sup> and terpene<sup>32-35</sup> series. Hydroboration-oxidation has been used to obtain alcohols from these compounds; stereospecific products are usually obtained, especially when alkylboranes are used in the hydroboration reaction.

By hydroboration with diisopinocampheylborane followed by oxidation, numerous optically active alcohols have been synthesized.<sup>36-38</sup> This procedure has been used to obtain alcohols from *cis*-, *trans*-, and cyclic olefins; the optical purities which resulted were 65-91%, 5-30%, and 37-67%, respectively.

#### AMINATION

In his study of the hydroboration reaction, Brown found that organoboranes react with chloroamine or with hydroxylamine-O-sulfonic acid to produce the corresponding amines.<sup>39</sup> The reaction is stereospecific, as with the alcohol synthesis; however,





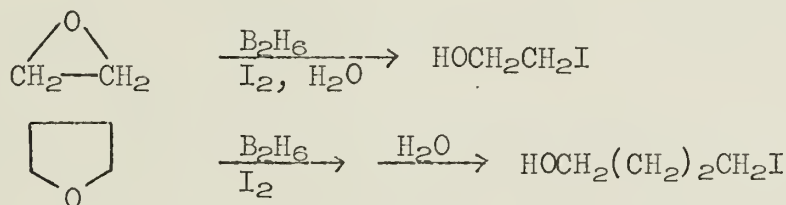
there are two disadvantages which presented no problem in the alcohol synthesis. Yields are lower, approximately 60%, and hindered olefins failed to react. It is possible to circumvent the second of these difficulties by the use of diglyme as a solvent in conjunction with hydroxylamine-O-sulfonic acid to obtain yields of 40-60% even with hindered olefins.<sup>40</sup> The stereospecificity of the reaction is illustrated by the conversion of 1-methylcyclohexene to trans-2-methylcyclohexylamine (60%).

By the use of diisopinocampheylborane in the hydroboration reaction, optically active amines of high optical purity can be synthesized by this method.<sup>41</sup>

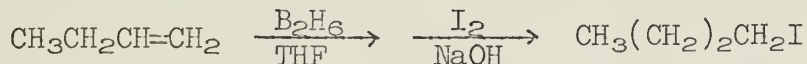
#### HALOGENATION

Aliphatic organoboranes are essentially inert toward the halogens. The reaction is slow and only one of the alkyl groups can be converted to the halide.<sup>1</sup> However, recently two interesting reactions with iodine have been reported.

Alcohols, ethers, and epoxides react with iodine in the presence of diborane to give the iodide.<sup>42,43</sup> The reaction proceeds rapidly at low temperatures to give yields of 70% or better.

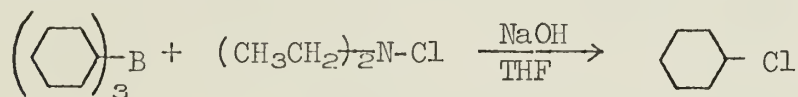


The reaction of organoboranes with iodine under basic conditions provides a simple synthesis of primary iodides.<sup>44</sup> The reaction is essentially complete in five minutes at room temperature. Yields of 30-65% are obtained. Advantage can be taken



of the fact that secondary alkyl groups, such as 2-butyl, react more sluggishly than primary alkyl groups. Thus by hydroborating terminal olefins with disiamylborane, yields of 90% or better can be obtained in the iodination reaction. The use of t-hexylborane which contains a tertiary carbon bonded to boron has not been investigated.

N-Chlorodialkylamines react with organoboranes as shown to yield 31-53% of the respective alkylchloride.<sup>45</sup>



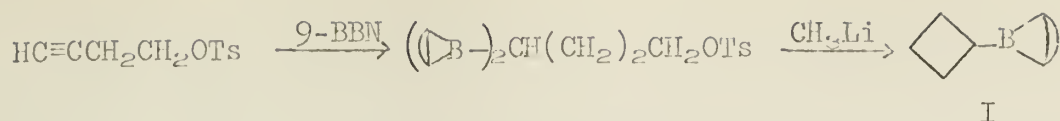
#### CYCLIZATION

Hydroboration of allyl chloride followed by treatment with base yields cyclopropane.<sup>1</sup> Improved yields can be obtained by the use of disiamylborane.<sup>21</sup> A wide variety of cyclopropyl derivatives has been obtained by this reaction in yields of 81-92%.<sup>46</sup> Thus 3,4-dichlorobutene on hydroboration with 9-BBN, followed by treatment with one equivalent of base gives an 81% yield of (chloromethyl)propane. All attempts

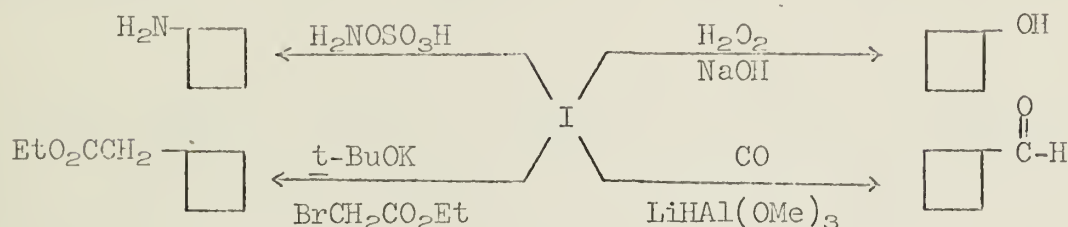


to produce cyclobutane by a similar method have failed. In the reaction illustrated, no cyclobutane is obtained. Brown<sup>47</sup> has been able to circumvent this difficulty and achieve the synthesis of cyclobutane derivatives by a method suggested by the work of Koster.<sup>48</sup> The B-cyclobutylbicyclo[3.3.1]nonane intermediate (I) can then be





subjected to various reactions to obtain cyclobutanes substituted with a variety of functional groups.

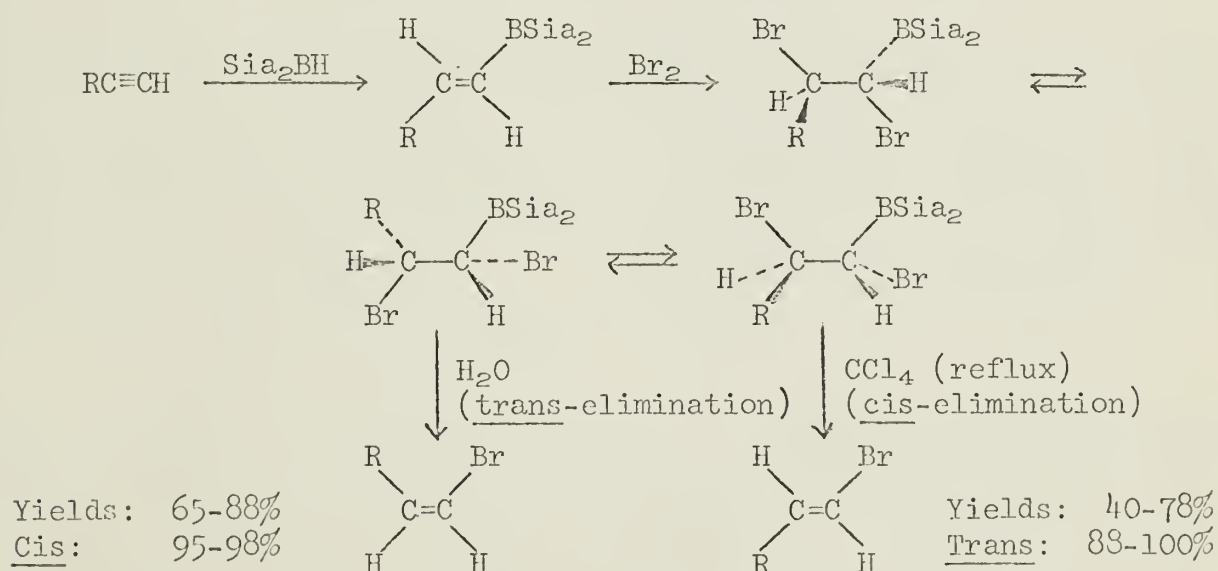


## OLEFIN SYNTHESIS

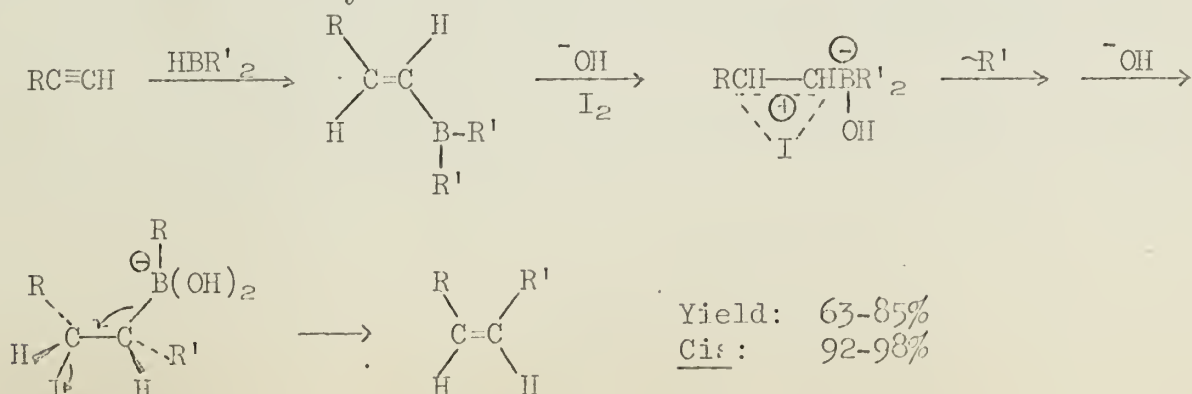
A combination of hydroboration-protonation can be used to convert alkynes to alkenes.<sup>1</sup> Protonation is accomplished by treatment of the intermediate vinylborane with a carboxylic acid. (Organoboranes are stable toward mineral acids and water.) If an internal alkyne is so treated, a quantitative yield of the cis-olefin is obtained. Disiamylborane is used for hydroboration, since diborane reacts preferentially with the vinylborane intermediate.

The new alkene syntheses that have resulted from the work of Brown and Zweifel are almost 100% stereospecific. These syntheses depend on two properties of organoboranes: (1) the elimination of haloboranes from  $\alpha$ -halosubstituted organoboranes and (2) the ability of boron to transfer an alkyl group to an adjacent carbon. In regard to the latter property, the migration of an alkyl group from boron to carbon has been shown to proceed with inversion at the migration terminus.<sup>49-53</sup>

Bromination of the intermediate vinylborane obtained from the hydroboration of an alkyne can be used to synthesize either a cis- or trans-product.<sup>54</sup>



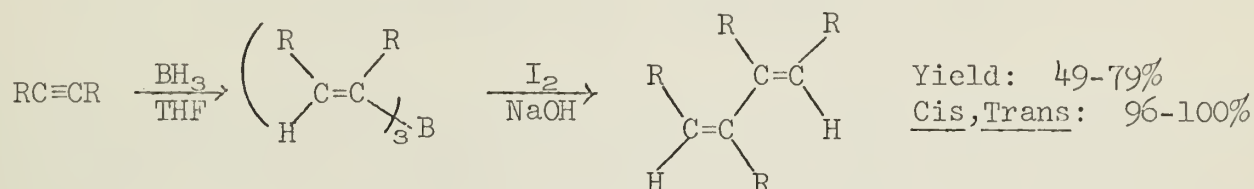
The stereoselective synthesis of substituted alkenes can be achieved by hydroboration-iodination of alkynes.<sup>55</sup>





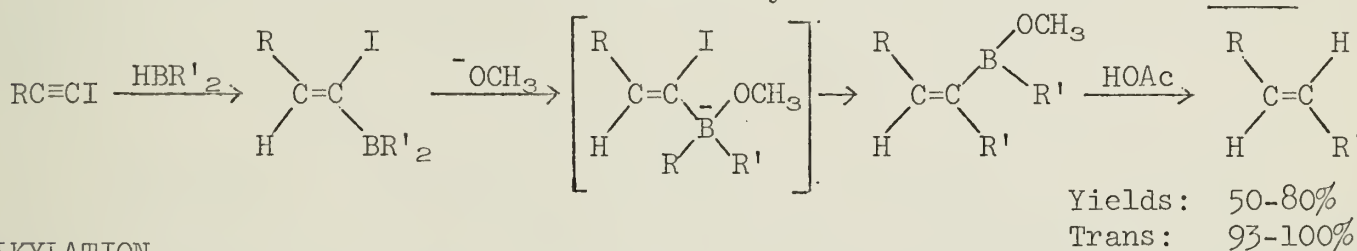
The utility of this reaction depends on the availability of the starting dialkylborane. Fortunately, most cyclic and many acyclic olefins are readily converted to substituted boranes. Consequently, this reaction offers an excellent route for the introduction of olefinic side chains.

The hydroboration of disubstituted alkynes with borane gives the corresponding trivinylboranes. Treatment of this intermediate with iodine and sodium hydroxide gives stereoselectively the cis,trans-conjugated diene by a mechanism similar to that of the above.<sup>56</sup> The hydroboration of 1-alkynes does not proceed to the trivinylborane stage. However, 1-alkynes react with hexylborane to give the corresponding



divinylhexylborane. Unfortunately iodination results in the migration of both the vinyl and the hexyl moieties. This can be avoided by the selective oxidation of the hexyl group with trimethylamine oxide.

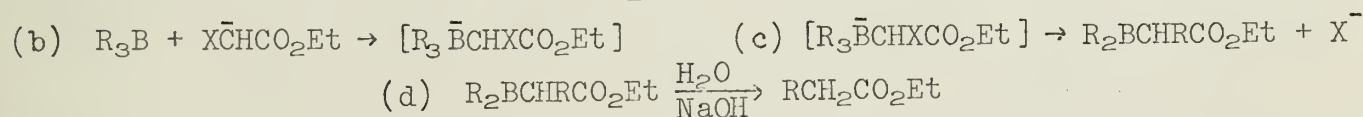
Zweifel also demonstrated that 1-haloalkynes can be converted to trans-olefins.<sup>57</sup>



## ALKYLATION

The alkylation reactions which occur by means of organoboranes can be divided into two broad categories on the basis of the mechanism involved. The first involves an alkyl transfer reaction from boron to carbon similar to those mentioned in the alkene synthesis. The second involves a 1,4-addition to a conjugated ketone or aldehyde similar to that seen in the Grignard reaction.

For the reactions in the first category, the following steps are probable: (a) formation of a carbanion or carbanion-like intermediate; (b) coordination of the intermediate with the trialkylborane; (c) rapid rearrangement of the resulting coordinated species; and (d) protonolysis of the organoborane derivative. Thus a general scheme can be written for this type of reaction where X is a good leaving group, such as bromide, nitrogen (N<sub>2</sub>), or dimethylsulfide. In this manner, ethyl



bromoacetate,<sup>58</sup> ylides,<sup>59-61</sup> and diazocompounds<sup>62-64</sup> have been alkylated. For the bromoacetate reaction, the carbanion is formed by treatment of ethyl bromoacetate with potassium *t*-butoxide; ylides and diazocompounds are used directly. The hydrolysis is unusually facile, because of the adjacent carbethoxy group. Acetone, acetonitrile, and ethyl acetate have been alkylated by this procedure. These syntheses have one major disadvantage, namely, that only one of the three alkyl groups of the organoborane is transferred.

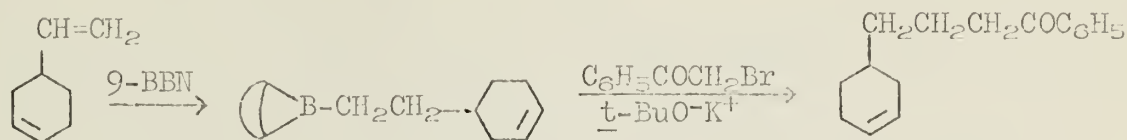
It was found that with ethyl dibromoacetate, two alkyl groups could be introduced at the  $\alpha$ -position.<sup>65</sup> Since the intermediate  $\alpha$ -alkyl- $\alpha$ -bromoacetate can be isolated, two different alkyl groups can be used.

Limited success was obtained in alkylating  $\alpha$ -bromoketones.<sup>66</sup> The susceptibility of these compounds toward condensation presented a major obstacle. Also sterically hindered organoboranes failed to react.

Two major synthetic improvements eliminated these difficulties. Migration of

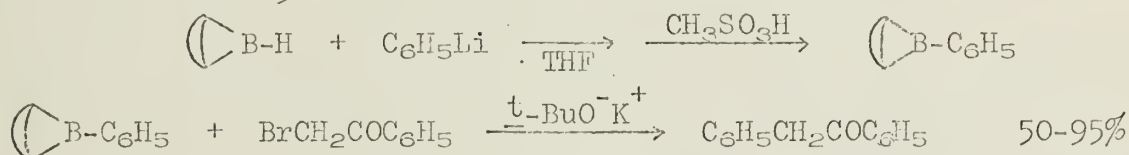


the cyclooctyl moiety in 9-BBN occurs very sluggishly. This by hydroboration with 9-BBN, yields of 40-90% based on the olefin can be obtained in the reaction with bromoacetate, dibromoacetate, and  $\alpha$ -bromoketones. This method fails with ylides and diazocompounds.<sup>67-68</sup> A further advantage of 9-BBN is the possibility of selective alkylation with a diene.

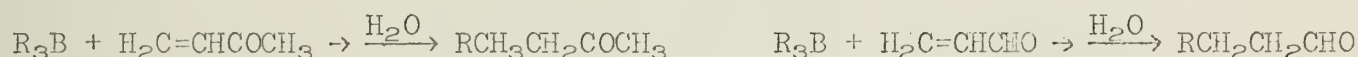


The second improvement is the introduction of a highly hindered base, potassium 2,6-di-*t*-butylphenoxide.<sup>69</sup> Possible condensation and other side reactions are avoided by use of this base. Improved yields are obtained in most reactions, especially with the ketones which are more susceptible to condensation. The use of this base also permits the facile synthesis of nitriles from organoboranes and chloroacetonitrile in yields of 65-95%. This reaction failed with potassium *t*-butoxide.

In a recent study Brown has extended this work to the  $\alpha$ -arylation of ketones and esters.<sup>70</sup> B-Aryl-9-BBN may be readily synthesized from the corresponding organolithium derivative and 9-BBN.



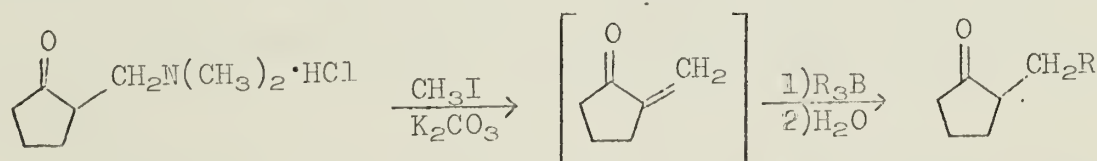
The second class of alkylation reactions, the 1,4-addition reaction, provides another synthetic alternative. Thus methylvinylketone and acrolein readily react with organoboranes to give methyl ketones and aldehydes, respectively.<sup>71</sup> The reaction



is complete in a few minutes at 25°; however, only one of the alkyl groups reacts.

This method can also be employed to prepare 2-bromoaldehydes from 2-bromoacrolein.<sup>71</sup> It is difficult to obtain this class of compounds by other means.

Another similar reaction is that between organoboranes and Mannich bases.<sup>71d</sup> Yields of 54-90%, based on the reaction of one alkyl group, are obtained in this manner.



Brown in a comprehensive study of alkylation reactions has demonstrated that all the reactions proceed stereospecifically with retention of the original stereochemistry of the boron-carbon bond.<sup>72</sup>

## SUMMARY

The chemistry of organoboranes has opened new doors in organic synthesis, and hydroboration provides the key. From one intermediate it is possible to introduce almost any functional group. Alcohols, amines, esters, nitriles, and ketones are easily obtained from alkenes. Even further, it is possible to obtain one-, two-, and three-carbon homologated derivatives. H. C. Brown and his co-workers have played a major role in the development of this field.



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## THE STRUCTURE OF LOMOFUNGIN

Reported by Craig D. Tipton

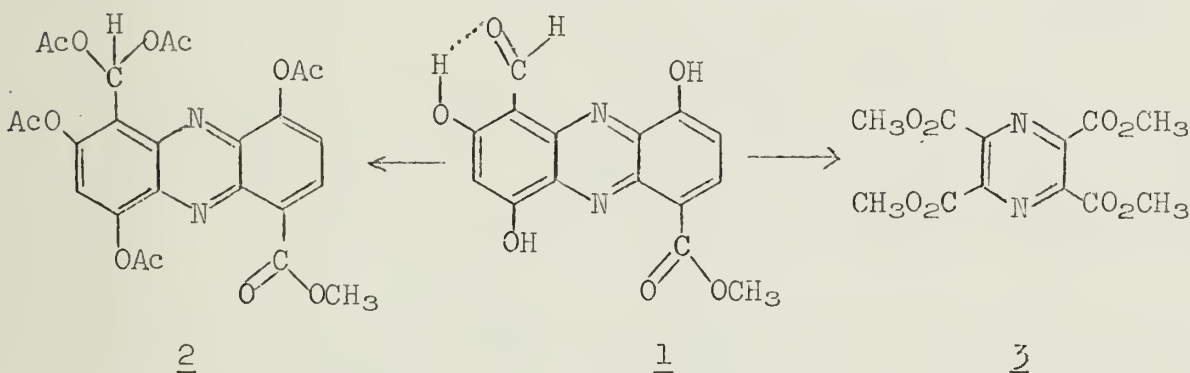
January 12, 1970

## INTRODUCTION

The antibiotic lomofungin has been recently isolated and characterized by Bergy and Johnson.<sup>1</sup> It was found to inhibit the growth of gram-positive and gram-negative bacteria, to have antifungal properties, and to promote the growth of mammals, birds, fish, and reptiles when used as a feed supplement. The substance is, however, too toxic to find promise as a therapeutic agent in medicine. Lomofungin is produced by *Streptomyces lomondensis*, is isolated by extraction, and final purification is by crystallization from dimethylformamide.

## DISCUSSION

Lomofungin is an olive-yellow crystalline compound that decomposes without melting at a temperature greater than 320°. As a result of degradative studies the structure of the antibiotic has been proposed as 1, 1-carbomethoxy-5-formyl-4,6,8-trihydroxyphenazine.<sup>2</sup>



Lomofungin has the molecular formula  $C_{15}H_{10}N_2O_6$  (M.W. 314) as indicated by elemental analysis and confirmed by high resolution mass spectrometry. The nmr spectrum of lomofungin in DMSO- $d_6$  shows seven of the ten hydrogen atoms in the molecule with a three proton singlet at  $\delta 3.95$ , an aromatic singlet at  $\delta 6.76$ , aromatic doublets at  $\delta 7.23$  and  $8.12$  ( $J = 8$  Hz), and a one proton absorption at  $\delta 11.01$ .

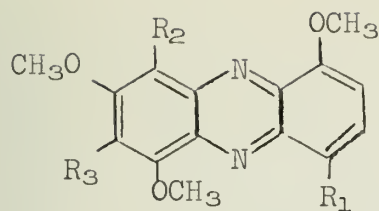
Acetylation of lomofungin with acetic anhydride-sulfuric acid gives a pentaacetate 2 whose ultraviolet spectrum limits the molecule to a linear three-ring aromatic system ( $\lambda_{\max}$  267, 364 m $\mu$ ,  $\epsilon_{\max}$  72,500, 19000 respectively).<sup>3-6</sup> The ring system is defined as a phenazine by oxidation of the antibiotic with refluxing concentrated nitric acid to 2,3,5,6-pyrazinetetracarboxylic acid. This compound was isolated and characterized as its tetramethyl ester 3 which gave a single nmr peak at  $\delta 4.05$ .

Methylation of lomofungin with methyl iodide and silver oxide in chloroform at 40° gave its trimethyl ether 4 whose nmr spectrum exhibited three new  $ArOCH_3$  singlets at  $\delta 4.14$ , 4.17, and 4.23. The other two substituents on the phenazine nucleus were concluded to be an aldehyde and a methyl ester. The aldehyde was indicated by the low field peak at  $\delta 11.28$  in 4 which did not exchange with  $D_2O$ . The methyl ester was indicated by the original  $-OCH_3$  singlet in 1, an infrared band at  $1730\text{ cm}^{-1}$  in 4, and the hydrolysis of 4 in 2 N sodium hydroxide to give an acid.

The presence of the aldehyde function was confirmed by reduction of 4 with sodium borohydride in methanol to give the alcohol 5 which had a  $-CH_2-$  singlet at  $\delta 5.39$ . Also obtained from this reaction was 6, the aromatic methyl ether of 5.

The substitution pattern of the ring bearing the formyl group is defined as shown in 1 by decarbonylation of 4 using chlorotris(triphenylphosphine)rhodium(I)<sup>7</sup> in refluxing benzonitrile to give 7 whose nmr spectrum contains an aromatic meta AB quartet ( $\delta 6.87$  and  $7.32$ ;  $J = 2.5$  Hz) in place of the one proton singlet at  $\delta 6.91$ . Since the aromatic proton generated on decarbonylation is that at lower field ( $\delta 7.32$ ), the formyl group was placed as shown instead of between the two methoxyl groups. This placement is also supported by the isolation of a fully aromatic C-methylated side reaction product 8 from the previous methylation of lomofungin which indicates an unsubstituted position between the hydroxyl groups of 1.





<u>4</u>	$R_1 = \text{COOCH}_3, R_2 = \text{CHO}, R_3 = \text{H}$
<u>5</u>	$R_1 = \text{COOCH}_3, R_2 = \text{CH}_2\text{OH}, R_3 = \text{H}$
<u>6</u>	$R_1 = \text{COOCH}_3, R_2 = \text{CH}_2\text{OCH}_3, R_3 = \text{H}$
<u>7</u>	$R_2 = \text{COOCH}_3, R_2 = \text{H}, R_3 = \text{H}$
<u>8</u>	$R_1 = \text{COOCH}_3, R_2 = \text{CHO}, R_3 = \text{CH}_3$
<u>9</u>	$R_1 = \text{COOH}, R_2 = \text{CH}_2\text{OCH}_3, R_3 = \text{H}$
<u>10</u>	$R_1 = R_3 = \text{H}, R_2 = \text{CH}_2\text{OCH}_3$
<u>11</u>	$R_1 = R_2 = \text{CH}_3, R_3 = \text{H}$

The substitution pattern of the ring bearing the carbomethoxy group in 1 is defined by the hydrolysis of 6 to give 9 which was decarboxylated over copper powder in pyridine at  $220^\circ$  to give 10. The nmr spectrum of 10 showed the presence of three aromatic protons on adjacent carbons ( $\delta 7.03$ ,  $J = 7.96$ ,  $1.22$  Hz;  $\delta 7.64$ ,  $J = 7.96$ ,  $8.56$  Hz;  $\delta 7.95$ ,  $J = 8.56$ ,  $1.22$  Hz) while the precursor 9 shows an ortho substitution pattern ( $\delta 7.16$ ,  $8.67$ ;  $J = 8.0$  Hz). Since H-1 in the spectrum of 10 must be the proton at  $\delta 7.95$ , the expected deshielding effect of the carboxyl group is only consistent with its placement at C-1 in 9 (H-2 at  $\delta 8.67$  in 9 vs.  $\delta 7.64$  in 10; H-3 at  $\delta 7.16$  in 9 vs.  $\delta 7.03$  in 10). The similar  $J_{23}$  coupling constants in the two compounds ( $8.0$  Hz in 9,  $7.96$  Hz in 10) is also consistent with this placement.

The substitution patterns of the terminal rings are also supported by the nmr spectrum of 11, obtained by prolonged lithium aluminum hydride reduction of 4 in refluxing tetrahydrofuran. In the nmr spectrum of 11 one of the aryl methyl groups ( $\delta 2.84$ d,  $J = 1.0$  Hz) is slightly split by an adjacent aromatic proton ( $\delta 7.45$ ·octet,  $J = 8.0$ ,  $1.0$  Hz) while the second aryl methyl ( $\delta 2.73$ s) found at nearly identical field, but with no adjacent hydrogens, is unsplit.

Structure 1 has been chosen over the other theoretically possible phenazine, 1-carbomethoxy-8-formyl-4,5,7-trihydroxyphenazine, on biosynthetic grounds since lomofungin is presumed to arise from oxidative coupling of two moles of 4-hydroxy-anthranilic acid. In this connection it is significant that a similar substitution pattern is found in the antibiotic griseolutein A.<sup>8</sup>

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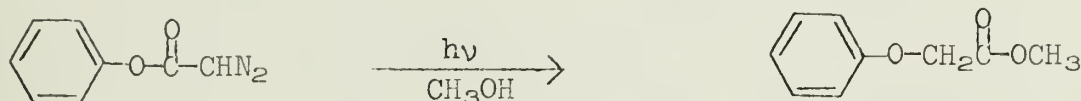


# REARRANGEMENT IN THE PHOTOLYSIS OF DIAZO ESTERS

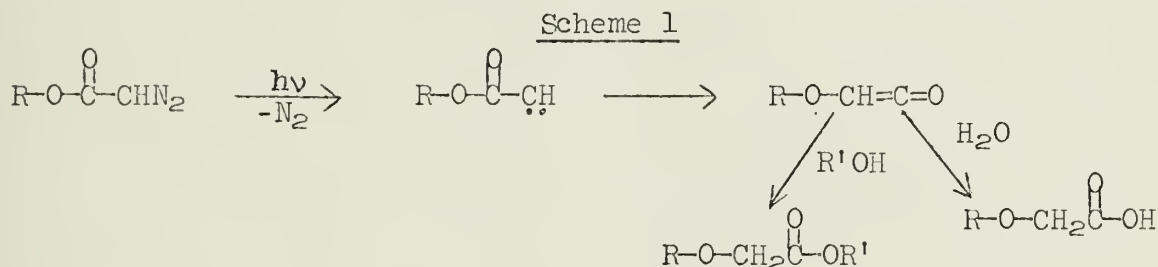
Reported by James Bittell

January 15, 1970

The first intramolecular reaction during the photolysis of diazo esters was reported by Westheimer, *et al.* in 1965.<sup>1</sup> They labeled the enzyme chymotrypsin at the active serine site by attaching a diazo ester. Photolysis of this diazoacetyl chymotrypsin followed by hydrolysis gave 42% carboxymethylserine, the product of rearrangement.<sup>2</sup> More recently the rearrangement upon photolysis of ethyl diazoacetate<sup>3,4</sup> and phenyl diazoacetate<sup>4</sup> has been studied. For example, photolysis of phenyl diazoacetate in methanol gives methyl phenoxyacetate in 45-60% yield.



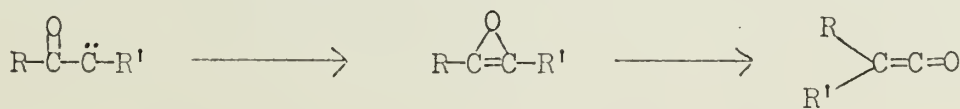
The mechanism suggested for the rearrangement of diazo esters (Scheme 1) is the same as that proposed for the analogous Wolff rearrangement of diazo ketones in the Arndt-Eistert synthesis.<sup>5</sup> The possibility of a carbonium ion intermediate produced



via protonation of either the photoexcited diazo compound or the carbene is considered unlikely.<sup>5</sup> Acid catalyzed decomposition of ethyl diazoacetate gives no rearranged product. Furthermore, photolysis of ethyl diazoacetate in 2-propanol solution of lithium bromide does not produce bromoacetate as might be expected if a carbonium ion is produced, and the yield of rearranged product is unaffected by the lithium bromide.

Some of the recent evidence concerning the mechanism of the Wolff rearrangement is pertinent, since it is the basis for the mechanism shown in Scheme 1. Wilds, *et al.*<sup>6</sup> suggested in 1965 that the solvent attacks the diazo ketone directly in the thermal Wolff rearrangement. It has also been argued that a free carbene may not be present and that the formation of ketene is concerted. Recent kinetic investigations of the thermal Wolff rearrangement have shown it to be first order in diazo ketone and essentially independent of the concentration of alcohols or amines.<sup>7,8</sup> A C<sup>14</sup> kinetic isotope effect may be expected if loss of nitrogen and rearrangement are concerted in the Wolff rearrangement. However, Yukawa, *et al.*<sup>9</sup> did not observe a C<sup>14</sup> kinetic isotope effect in the silver benzoate catalyzed Wolff rearrangement of  $\alpha$ -diazoacetophenone labeled at either the carbonyl carbon or the phenyl group.

The mechanism of the isomerization of the  $\alpha$ -keto carbenes to the ketene structure may involve an oxirene intermediate, at least in the gas phase. Recent data obtained by Strausz<sup>10</sup> on the gas-phase photolysis of symmetrical and asymmetrical C<sup>13</sup>-labeled  $\alpha$ -diazo ketones suggests the oxirene intermediate. However, earlier work by Franzen<sup>11</sup> on C<sup>14</sup>-labeled azibenzil seemed to rule out the oxirene intermediate for the photochemical and the thermal rearrangement in solution.



oxirene



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